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Deadline for Abstracts June 13, 1958

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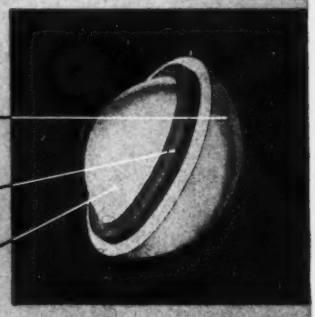

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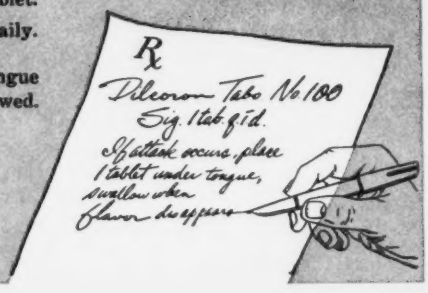

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MAY 1958
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OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Editorial

How to Write an Abstract

June 13, 1958, is the deadline for abstracts of papers that are to be submitted for presentation at the Annual Scientific Sessions of the American Heart Association in October. These abstracts are the basis for selection of the program by the committee and they are also widely read. It therefore seems appropriate at this time to publish this editorial on "How to Write an Abstract."

An abstract should be made as informative as possible within its given limitations. Good work suffers seriously if an abstract is poorly written. The abstract is the only evidence available to the screening committee that selects the program.

The printed abstracts are widely circulated and read by many who cannot attend the meeting. To crystallize experimental findings into a concise, lucid, and well-organized statement is an achievement; it results in intellectual gratification to both author and reader.

A good abstract indicates briefly the purpose of the investigation and the methods used, and presents precisely the new data (if necessary in relation to those already in the literature).

George E. Burch in his helpful essay, "Of Publishing Scientific Papers," warns that "the scientific character of a man is identifiable in his writings and often assists in evaluation of his work by others." Burch urges that only clear, definite statements be made. The author should remember that he has all the data, whereas the reader has only those presented in the abstract or paper.

Some practical suggestions may be offered to the abstract writer. Anatole France used to subject his work to five successive forms of corrections, as follows:

1. Weed out the who's, which's, and whom's.
2. Shorten sentences. Strike out phrases linking sentences. Make sound transitions of thought.
3. Watch the order in sentences; recurrence of the same word means that the sentence should be rewritten, not that a synonym should be used.
4. Take out useless adjectives.
5. Clip away the pastry, the adventitious, and the redundant.

These recommendations were quoted by Alan Gregg, who added the following reflection: "Clear thinking does not always produce clear writing (though it usually does), but logical, discriminating, conclusive, precise, clear writing comes only from an orderly, critical, clear, and alert intelligence."

Gregg then offered one last bit of advice: He suggested that one read an abstract aloud to oneself several times, correcting and polishing. Then read it to someone else. The incomprehensible passages, the fallacious assumptions, the useless and inexact words—all the worst faults—will stand out.

One of the greatest of French writers, Gustave Flaubert, said: "Si vous caressez votre phrase assez longtemps, elle finira par sourire." If you caress your sentence long enough, it will at last smile.

ROBERT W. WILKINS

The Lewis A. Conner Memorial Lecture

Rheumatic Heart Disease—A Challenge

By CHARLES H. RAMMELKAMP, JR., M.D.

PROGRESS in medical and allied sciences has been so rapid in the past few decades that it is advisable to review the accumulated data so that those responsible for the health of the population may apply the most effective procedures. In the field of cardiovascular disease, the introduction of antibiotic medications has resulted in the rapid development of therapeutic regimens that have altered the prognosis of at least 3 major diseases affecting the cardiovascular system. They are rheumatic and syphilitic heart disease and bacterial endocarditis. Since the physician now has reason to be confident of his ability to manage these diseases, we are approaching a period where interest in them is declining, and emphasis has shifted to the study of hypertension and the degenerative diseases of the heart and blood vessels. Although such emphasis will and should continue to prevail, it is important to recognize that cardiovascular disease related to infection is still responsible for many deaths and considerable morbidity. In this Conner lecture some of the recent studies pertaining to rheumatic heart disease will be summarized in an effort to direct attention toward more effective control procedures and to emphasize certain limitations in our knowledge of this disease.

Before discussing control or therapeutic measures, it is first necessary to review certain facts pertaining to rheumatic heart disease. Rheumatic valvular heart disease is a sequela of acute rheumatic fever and is known to develop in approximately 50 to 70 per cent of patients who exhibit the latter disease.[1] Acute rheumatic fever, in turn, may be considered a sequela of acute respiratory infection caused by group A streptococci. From published data it is evident that the attack rate of rheumatic fever following a proved streptococcal infection varies between 2 and 3 per cent.[2] This attack rate in the population appears to be fairly constant (excluding, perhaps, the first experience with a streptococcal infection) and is independent of the infecting type of streptococcus.

Figures on the incidence of streptococcal infections, acute rheumatic fever, or rheumatic heart disease are not available in this country, but it is generally believed that the rates for all 3 have been decreasing for several decades. The exact number of individuals in the population with rheumatic valvular disease is unknown, since the prevalance varies according to age, geographic area, and diagnostic criteria employed.

Specific data concerning the incidence of acute rheumatic fever have been maintained in Denmark and Norway and are presented in figure 1.[3, 4] In both these countries the attack rates have been decreasing for several decades. From the data presented in figure 2, where the attack rates for acute rheumatic fever among urban and rural populations are compared, it is apparent that the decline is greatest among individuals dwelling in the city. In contrast to these reports, the incidence of acute rheumatic fever in certain urban areas such as in Santiago, Chile, as determined by admissions to hospitals, has not shown such a remarkable decline.[5] These ob-

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Many of the studies reviewed in this report were sponsored by the Commission on Streptococcal Diseases and the Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board, and were supported by the Offices of the Surgeons General, Departments of the Army and the Air Force, Washington, D. C., and the Cleveland Area and Greene County Heart Associations.

Given at the meeting of the American Heart Association, Chicago, October 26, 1957.

servations, meager as they may be, suggest that the decreased incidence of acute rheumatic fever cannot be ascribed to procedures employed by physicians but, rather, to factors exerting an influence on the spread of infections in general.

One approach to the control of rheumatic valvular heart disease in any population is to focus efforts on the inciting agent and, from knowledge of the natural history of the disease, consider those points that are vulnerable to an aggressive attack by the physician. Since the basic cause of the valvular deformity is an infection caused by the group A streptococcus, the approach employed by the epidemiologist for the control of infections should be especially rewarding. Thus, the first consideration will be directed toward 3 problems in relation to the inciting agent: elimination of the reservoir of infection, interruption of the pathways of transmission of group A streptococci, and increasing the resistance of the host. Subsequently, consideration will be directed toward the patient with an acute streptococcal infection, with acute rheumatic fever, and, finally, with established valvular heart disease.

Group A Streptococcus

Reservoir of Infection. The lymphoid tissue of the upper respiratory tract of man is the reservoir for the group A streptococcus. Here, under optimum conditions the organism can multiply freely. Evidence permitting accurate description of the methods by which group A streptococci are brought to the nasopharyngeal reservoir and the resulting reaction of the host to this invasion is incomplete and sometimes conflicting. Therefore, it would seem pertinent to review the current concepts of the natural history of streptococcal infection.

The streptococcus enters the host through the nose and occasionally through the mouth. Most streptococci that are inhaled are eliminated rapidly by the normal defense mechanisms of the respiratory tract. Those that survive and multiply produce M protein, the substance responsible for the virulence and serologic type-specificity of the organism.

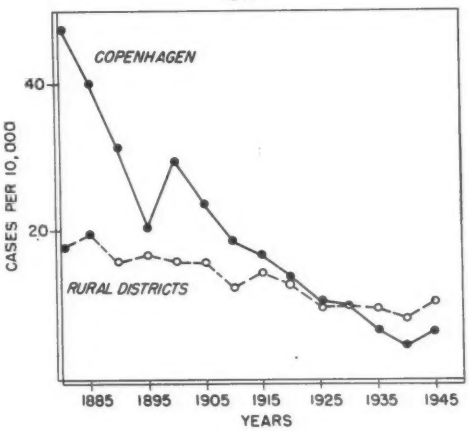

Fig. 1 *Top.* Rheumatic fever in Denmark and Norway.

Fig. 2 *Bottom.* Rheumatic fever in city and rural populations.

When streptococci begin to multiply, the lymphoid tissues become inflamed and the majority of patients develop symptoms of a respiratory illness. However, both asymptomatic and mild streptococcal infections are known to occur, as indicated by the observations that 15 per cent of patients with rheumatic fever give no history of a preceding respiratory illness and another 25 per cent experience an antecedent illness so mild that neither patient nor physician suspects the nature of the disease.[6] Because of these variations in the clinical nature of streptococcal disease, one of the best methods for estimating

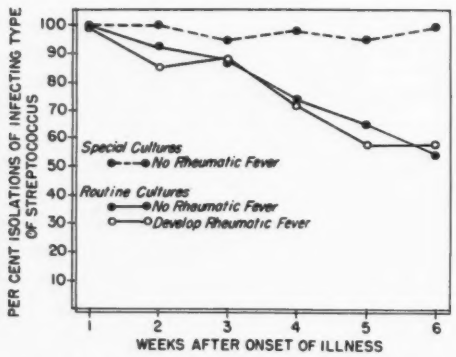

FIG. 3. Isolations of streptococci following an untreated streptococcal infection.

the number of cases of infection in a population is the enumeration of new cases of rheumatic fever. (These calculations are valid only when patients receive no therapy with antibiotics for the acute respiratory illness.)

Following experimental inoculation of the respiratory tract with typable group A streptococci, cultures of the oropharynx usually show no streptococci until a few hours before the onset of symptoms. Once the acute disease becomes manifest large numbers of organisms are readily isolated from cultures of both the nose and throat. As shown in figure 3, group A streptococci are usually isolated from only 50 to 60 per cent of patients 6 weeks after the acute illness. These results are obtained when routine methods are employed in patients who develop rheumatic fever and in those who fail to exhibit signs of a nonsuppurative complication. Such studies have led to the concept that the convalescent carrier state is of short duration. Likewise, the relatively small number of isolations from rheumatic subjects has been considered as evidence that rheumatic fever may be caused by agents other than the group A streptococcus. In addition, these data lead to the supposition that the isolation of group A streptococci from the respiratory tract is indicative of a recent streptococcal infection.

That this general concept of the carrier state is false is shown by the data presented in figure 3, which is representative of information obtained in an extensive survey.[7] If multiple cultures and special bacteriologic technics are employed, group A organisms can be recovered from all patients 6 weeks after the onset of an uncomplicated streptococcal illness. Likewise, when similar technics are applied to the study of patients with acute rheumatic fever, the organism can be isolated from most patients.[8] In one study where special cultures were obtained at least 17 weeks after recovery from an attack of tonsillitis or pharyngitis, 97 per cent of the patients were shown to be carrying the infecting type of streptococcus.*[9] Thus, we can reasonably assume that the carrier state actually persists for months and perhaps years, but the number of organisms present in the lymphoid tissues is so small that routine bacteriologic studies fail to detect them.

Since the carrier state is prolonged, it is important to understand the biology of the organism during its residence in the respiratory tract and to determine the role of the carrier in the maintenance of the disease in the population. Here again definitive data are meager, but certain facts are available which may serve as guides in the establishment of control measures.

Immediately following infection and during the convalescent carrier state, there are quantitative and metabolic changes in the streptococci that undoubtedly play a role in the spread of disease. As shown in figure 4 in pictorial form, the number of streptococci present in the respiratory tract decreases rapidly as convalescence progresses. Likewise, streptococci that may be isolated in large numbers from the nasal secretions during the first 3 weeks disappear rapidly in the absence of signs of paranasal suppuration. Beginning about the fourth or fifth week, streptococci isolated from the oropharynx exhibit a progressive loss of ability to elaborate M protein so that they are no longer typable. In the

*Most of the streptococci isolated at this time were not typable, but restoration of type-specificity by serial passage in mice indicated that they were derived from the original infecting strain.

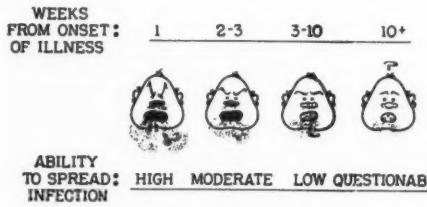

FIG. 4. Transmission of streptococcal infections.

study presented here nontypable variants were isolated from 70 per cent of carriers by the fifth month of convalescence.[7, 9]

These changes in numbers of streptococci, their location and persistence in the respiratory tract and loss of ability to elaborate M protein are important factors that influence the incidence and maintenance of streptococcal infections in the population. The studies of Wannamaker (fig. 4) have demonstrated that the ability to transmit disease to other individuals is high during the first 3 weeks of infection, when many typable streptococci are present in the secretions of both the nose and throat.[10] As the carrier state continues, the ability to transmit disease decreases, and it appears likely that the individual harboring a few streptococci is not an important source of infection. In support of this suggestion are the observations of Rothbard and Watson[11] and Krause[12] demonstrating that typable strains of group A streptococci isolated from carriers readily produce infections when introduced into the respiratory tract of monkeys, whereas strains that no longer elaborate M protein do not parasitize these animals. Thus, most convalescent carriers who harbor small numbers of attenuated streptococci probably do not serve as a reservoir of infection.

The only effective method available for the elimination of the reservoir is by treatment of the carrier with potent antibacterial agents. Theoretically, by means of mass bacteriologic surveys carriers can be identified and streptococci eliminated from the population by appropriate procedures. However, such methods are not practical because of the dynamic nature of the disease and the inadequacies of the bacteriologic technics. As a result, mass elimination of the reservoir of infection has been employed only in military populations, where treatment can be administered to all individuals. Originally, sulfonamide drugs were used, but it was soon demonstrated that epidemics recurred as soon as the population ceased taking medication.[13] These results were not surprising, since the sulfonamides are bacteriostatic and treatment of infection is not followed by elimination of the organism from the respiratory tract. In contrast, when penicillin is administered for at least 10 days to convalescent carriers, streptococci are eradicated from the majority of carriers.[14]

In civilian populations mass elimination of group A streptococci is not feasible; therefore, the practicing physician must employ other methods. Since the patient with an acute infection is especially likely to spread disease during the illness and during the early convalescent period, it is important to eliminate this source of streptococci. Here again, the sulfonamides are ineffective; rather, penicillin should be administered for at least 10 days to eradicate the organism effectively. The administration of antibiotics for shorter periods will control the acute respiratory symptoms, but usually will not eliminate the streptococcus. In addition, the physician who sees a patient with a streptococcal infection should examine and culture the family contacts. By treatment of contacts that show positive cultures or exhibit signs of a recent respiratory infection, inapparent sources of infection may be controlled.

Transmission of Infection. One of the most effective methods used in the control of infections is the blocking of the pathways of transmission. Group A streptococci, as well as other agents causing respiratory disease, are thought to be transferred by both indirect and direct routes. The indirect or airborne transfer of streptococci has been emphasized in recent decades because of the demonstration of large numbers of organisms in air samples, and on bedding, clothing, dust, and other articles in the environment where the population is experiencing a streptococcal epi-

TABLE 1.—*Relationship of Recurrent Attacks of Rheumatic Fever to Valvular Heart Disease**

Number of recurrences	Number of cases	Valvular heart disease
		per cent
0	361	21
1	109	34
2 or more	48	46

*Biörck[20]

demic. Although direct evidence indicating the successful transfer of infection from these reservoirs through the air was lacking, several attempts were made to control environmental contamination. Thus, aerosols, ultraviolet light, and treatment of bedding, clothes, and dust have been employed, but in each instance respiratory infections, including those caused by the streptococcus, have not been controlled.[15]

The true epidemiologic significance of environmental reservoirs was recently clarified by Perry.[16, 17] Blankets contaminated by patients with streptococcal infections were distributed to a large number of normal subjects but no infections resulted. Likewise, dust contaminated with group A streptococci collected from floors of military barracks failed to produce disease when inoculated into the respiratory tract of volunteers. Subsequently, it was demonstrated that group A streptococci in secretions of patients with active streptococcal disease were noninfectious after the specimen was dried.[18] Since the organisms were still viable, these data again emphasize that the mere isolation of streptococci from a carrier or from the environment does not establish the importance of these reservoirs in the spread of disease.

The studies of Wannamaker[10] show that the major pathway of transmission is by direct or intimate contact. Prevention of intimate contact is difficult to accomplish, but improved economic standards in the population with the associated decrease in crowding in homes and schools should achieve more than any effort expended by the physician. It seems entirely possible that decreasing opportunities for direct transmission of the organism resulting from improved economic conditions may be responsible for the observed decline of rheumatic fever in the United States and the Scandinavian countries.

Susceptible Host. Finally, in the control of infectious diseases the susceptible host should be examined in an effort to determine whether or not resistance to infection can be increased. Tonsillectomy has been recommended for this purpose but this procedure does not prevent streptococcal infections nor does it reduce the attack rate of rheumatic fever. Indeed, tonsillectomy may even increase the risk of developing rheumatic fever because the absence of tonsils makes the diagnosis of a streptococcal infection more difficult, and specific chemotherapy is thereby likely to be omitted.[19]

Resistance against streptococcal infections can be maintained by continuous prophylaxis with the sulfonamide drugs or penicillin. Such measures cannot be employed in the total population, but in selected patients their use is *obligatory* and *effective*. Streptococcal infections that develop in individuals who have already had an attack of acute rheumatic fever are especially likely to be followed by a recurrence of the complication. Since the ultimate prognosis and the incidence of valvular heart disease are related to the number of recurrences (table 1), this special group of patients should be protected against further infection by group A streptococci.[20] The most effective method for the continuous protection of the rheumatic subject is the intramuscular administration of 1,200,000 units of benzathine penicillin at monthly intervals.[21] The daily ingestion of sulfadiazine or penicillin will also prevent infection, but it requires complete cooperation by the patient.

The classical method for increasing the resistance of the host is immunization. Streptococcal infection in man is followed by a high degree of immunity, but this protection is type-specific and no heterologous resistance can be demonstrated.[10] Acquired type-specific antibodies persist for years, so that immunization may prove a feasible procedure.[22]

The use of suspensions of killed group A streptococci as antigen is attended by severe reactions.[23] Injections of partially purified M protein in man produce only moderate reactions, and, in a few instances, antibody formation has been demonstrated.[24] These studies are encouraging and should be extended because, if they are successful, immunization with vaccines containing mixtures of purified M proteins can be accomplished and continuous prophylaxis of the rheumatic patient would not be required.

Streptococcal Infections

Once a streptococcal infection becomes manifest, the practicing physician must consider specific therapy of the illness as well as the elimination of a reservoir of infection. There are several drugs known to exert a favorable effect on the course of the acute respiratory illness and the incidence of suppurative complications. Because the patient is primarily concerned with the acute phase symptoms, the physician frequently forgets that the major goal of therapy is the prevention of the remote complications, acute rheumatic fever, rheumatic heart disease, and acute nephritis. Therapeutic measures are available, which, if properly applied, will reduce the number of these nonsuppurative sequelae.

Major problems in effecting a reduction in the incidence of rheumatic fever are recognition of the streptococcal infection both by the patient and by the physician and the establishment of adequate therapeutic measures. Patients and physicians consider these infections to be a common cause of respiratory disease. Data presented in table 2 show the results of a study of all respiratory illnesses occurring in a group of families residing in Cleveland.[25] Both clinical and bacteriologic observations were made at weekly intervals and during each illness. These figures demonstrate that streptococcal infections are not a common cause of respiratory illness. In 1948 they represented about 1 per cent of the total respiratory illnesses. However, these rates are variable. In 1950, 3 per cent of the illnesses were caused by group A streptococci and one fifth of the population experienced the disease.

Table 2.—*Frequency of Streptococcal Illnesses in Cleveland**

Years	Person years	Respiratory illnesses		Number of illnesses per person per year	
		Strep.	Other	Strep.	Other
1948	173	14	1104	0.08	6.38
1949	232	40	1602	0.15	6.12
1950	264	53	1615	0.20	6.12

* From Dingle et al.[25]

Since all respiratory illnesses cannot be observed by a physician, it is important to train the patient to seek medical advice whenever a respiratory infection is associated with fever, soreness on swallowing, or tenderness at the angles of the jaw. These symptoms, or combinations of them, are present in 60 to 80 per cent of all streptococcal infections. The physician is assisted in making a presumptive diagnosis by obtaining a history of rapid onset of illness, the finding of tender and enlarged cervical lymph nodes, and exudative lesions on the tonsils or lymphoid tissues of the oropharynx. Two procedures that are not widely employed assist in the differential diagnosis of streptococcal infections. Enumeration of the leukocytes is helpful because most patients with streptococcal infections exhibit a leukocytosis whereas in the common viral infections normal leukocyte counts are noted. A definitive diagnosis can be made only by the isolation of beta hemolytic streptococci. When oropharyngeal swabs are cultured on sheep blood agar plates, large numbers of beta hemolytic colonies are observed. Bacteriologic procedures should be employed more frequently, and it is the duty of the physician to insist that adequate laboratory facilities be made available.

Once it is decided that the patient probably has a streptococcal infection, the method of treatment becomes important. The first observations on the effect of treatment of streptococcal infections in the prevention of acute rheumatic fever were made in 1948 by Massell,

TABLE 3.—*Effect of Eradication of the Infecting Type of Streptococcus by Specific Therapy on the Attack Rate of Rheumatic Fever*

Bacteriologic results	Number of patients	Rheumatic fever	
		Number	Per cent
Streptococci eliminated*	3,552	9	0.3
Streptococci present*	1,141	32	2.8

* As determined by a single culture 3 to 5 weeks after onset of the streptococcal illness.

Dow, and Jones,[26] who found that penicillin treatment of infections in rheumatic subjects prevented recurrences of rheumatic fever. Since that time adequate information has been obtained to establish the fact that treatment of acute streptococcal respiratory disease significantly reduces the attack rate of acute rheumatic fever. However, as experience accumulated, a number of failures have been observed.

The cause of such therapeutic failures has become evident from an analysis of 4,693 patients with group A streptococcal infections who received treatment with one of the antibacterial agents for at least 5 days[27] as demonstrated in table 3. In this study, if the infecting strain of streptococcus was not eliminated by therapy, the attack rate for rheumatic fever was 2.8 per cent, which was similar to the rate observed in patients who received no specific treatment. If the organism was eradicated, the attack rate was reduced tenfold to 0.3 per cent. Other information indicates that 9 patients in this study who developed rheumatic fever in spite of therapy probably continued to harbor the streptococcus, but the single routine culture obtained failed to show the organism.

These studies emphasize that elimination of the organism is not only important from the standpoint of control of infections, but eradication is *essential* if rheumatic fever is to be prevented. In order to accomplish this objective, therapy must be continued for several days after the patient has recovered from the acute respiratory illness. The most economical and effective measure is the administration of a single intramuscular injection of from 600,000 to 1,200,000 units of benzathine penicillin. Oral penicillin or other antibiotics must be given in full dosage for at least 10 days to be effective. When oral therapy is employed for only 5 days, which is the average duration of a streptococcal illness, many failures are observed. The sulfonamide drugs should never be used for treatment of acute streptococcal infections, since they do not alter the convalescent streptococcal flora of the respiratory tract, and they do not prevent rheumatic fever.[28]

Since treatment with penicillin is effective in preventing rheumatic fever even when instituted after the patient has recovered from signs of the acute illness,[29] the physician would be well advised to start therapy in all family contacts who give a history of a sore throat within the past 10 days or who show a positive streptococcal throat culture. This practice would also tend to decrease the possibility of spread of infection to others in the community.

ACUTE RHEUMATIC FEVER

Following the acute infection, the next stage in the natural history of streptococcal disease may be the development of acute rheumatic fever. Here, the possibility of preventing rheumatic heart disease by treatment of the acute rheumatic episode has been emphasized even less frequently than the prevention of rheumatic fever by therapy of the acute streptococcal infection. Historically, the patient and the physician have been concerned with the acute rheumatic symptoms and, since treatment with aspirin controls these manifestations, both parties have been made to feel secure. More recently, therapy with cortisone has been shown to exert a similar analgesic and antipyretic effect and again, we have found it difficult to maintain our interest in investigation of new methods that might decrease the incidence of subsequent rheumatic valvular heart disease.

However, 2 recently developed methods of therapy may possibly exert a favorable effect in the valvular lesions. The first of these methods is the early treatment of acute rheu-

TABLE 4.—*Effect of Treatment of Acute Rheumatic Fever on Valvular Heart Disease Eight Months After the Institution of Therapy*

Classification of murmur	Aspirin (96 pts.) per cent	Cortisone (76 pts.) per cent
No murmurs	49.0	73.7
Murmurs	51.0	26.3
mitral	37.5	25.0
aortic with or without mitral	13.5	1.3

matic fever with cortisone. The most extensive experience with this drug was reported by the cooperative study group sponsored by the American Heart Association and the Medical Research Council of Great Britain.[30] In a comparison of 167 children receiving cortisone with 168 children treated with aspirin no significant difference in the incidence of rheumatic valvular heart disease was observed 1 year after the acute disease. In contrast to these results are those obtained by the staff of the Streptococcal Disease Laboratory in a study conducted among male military personnel.[31] In this study, as shown in table 4, treatment with cortisone appeared to exert a favorable effect on valvular heart disease. The methods employed in this study were similar to those used in the cooperative study. Other than the fact that all patients were young adult males, the major difference between the 2 studies was the time that therapy with cortisone or aspirin was instituted. The majority of the military patients were treated within 7 days of the first rheumatic symptom and practically all were treated within the first 2 weeks. In the cooperative study relatively few patients were treated during the first week of illness. These data indicate that early treatment of acute rheumatic fever with cortisone may alter the development of valvular heart disease.

In view of the fact that major gains in the control of rheumatic fever and valvular heart disease have come through knowledge of the role of the group A streptococcus as the inciting agent, it is surprising that more attention has not been directed toward this organism in the treatment of the patient with acute rheumatic fever. Specifically, it is possible that treatment of acute rheumatic fever with penicillin might alter the severity of valvular heart disease. The reasons for such an hypothesis may be listed as follows. Rheumatic fever and rheumatic valvular heart disease are caused by infection with group A streptococci. Indeed, these organisms have been isolated by 3 groups of investigators from the involved valvular tissues in patients dying during an acute attack of rheumatic fever.[32-34] Treatment of streptococcal infections alters the attack rate of acute rheumatic fever even when administered 9 days after the onset of an acute respiratory illness.[29] As mentioned previously (table 3), failure to prevent rheumatic fever occurs when the infecting organism is not eliminated from the oropharynx. In addition, the impression has been obtained from preliminary studies that if penicillin is withheld for 1 week from patients with acute rheumatic fever, the incidence of subsequent valvular heart disease is higher than anticipated.[31] Finally, it would appear that chronic *progressive* rheumatic heart disease has become relatively rare in those countries where antibiotics are widely employed. All of these considerations indicate that unless acute rheumatic fever is a disease where maximal cardiac damage occurs during the first few hours of illness, the continued presence of the group A streptococcus in the oropharynx or perhaps even within the heart valves might contribute to the degree of valvular damage. Therefore, it would appear logical to recommend an intensive course of therapy with penicillin for all patients with acute rheumatic fever. Controlled studies at the University of Chile are now in progress to test the effect of such therapy on the incidence of valvular heart disease.[35]

RHEUMATIC VALVULAR HEART DISEASE

Finally, we come to the patient with valvular heart disease. As mentioned previously, these patients are subject to repeated attacks of acute rheumatic fever, and, therefore, they should be placed on continuous prophylaxis against streptococcal infections. This preven-

tive therapy should be continued indefinitely, especially in those individuals who experience frequent contacts with young people who are more likely to experience streptococcal infections.[36, 37]

There are 2 areas in preventive medicine that should be explored in relation to the patient with valvular heart disease. Members of the local heart associations should urge hospital staffs and physicians to establish a registry of all patients who have been observed with an attack of acute rheumatic fever during the past 30 years. These patients should be examined and those showing any signs of valvular heart disease should be placed on prophylaxis. In addition, surgical intervention may be recommended for those patients requiring this procedure.[20]

If continued valvular damage in the patient with rheumatic heart disease is not entirely due to scarring secondary to inflammation occurring during the acute rheumatic attack, there is a possibility that the physician can alter the course of this process. Many patients with chronic valvular heart disease exhibit high titers of antistreptolysin. Some of these patients show a few beta hemolytic streptococci on throat culture, whereas from others this organism has not been isolated. From unpublished experience there is evidence supporting the hypothesis that elevated antistreptolysin titers occur primarily among chronic carriers of group A streptococci. This is true even though the numbers of organisms obtained from throat cultures is small. If the continued presence of the streptococcus is responsible for smoldering rheumatic activity, all patients with chronic valvular heart disease who exhibit high titers of antistreptolysin should receive an intensive course of penicillin. Subsequently, they should be placed on maintenance prophylaxis.

In conclusion, effective control of rheumatic valvular heart disease has not been achieved. The contemporary physician is able to attack multiple vantage points and thereby interrupt the natural progress of streptococcal infections and their complications. Most of the successful procedures have been developed from knowledge of the natural history of group A streptococcal disease. Investigations of the pathogenesis of acute rheumatic fever and chronic valvular heart disease may reveal that the living streptococcus plays an important role, and by the removal of this organism further progress of valvular disease may be terminated. Thus, the final control of this major form of heart disease appears within reach. The challenge to us as a profession is to implement the program and to stimulate further investigation.

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Changes in the Serum Cholesterol and Blood Clotting Time in Men Subjected to Cyclic Variation of Occupational Stress

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With the technical collaboration of Russell J. Tat, M.D.

Accountants were selectively chosen as a self-controlled group for studying effects of cyclic occupational stress upon serum cholesterol and blood clotting time, since their routine work schedule is interrupted by urgent tax deadlines, associated with severe occupational stress. Forty male accountants (age 28 to 56) were bled biweekly for serum cholesterol and monthly for blood clotting time from January to June 1957. Complete records also were kept of weight, exercise, diet, relative work load, and any exposure to unusual avocational stress. When studied individually, each subject's highest serum cholesterol consistently occurred during severe occupational or other stress, and his lowest at times of minimal stress. The results could not be ascribed to any changes of weight, exercise, or diet. Marked acceleration of blood clotting time consistently occurred at the time of maximum occupational stress, in contrast to normal blood clotting during periods of respite. The possible implications of these results are discussed in relation to the problem of clinical coronary artery disease.

IF THE present high dietary intake of fat by upper class, middle aged Western man is chiefly responsible for his increased susceptibility to clinical coronary artery disease, then the relative immunity enjoyed by his female counterpart can only be explained by her failure to ingest a similar high-fat dietary or by her possession of some sex-linked protection against the presumed atherogenic qualities of a high-fat intake. However, when we studied the actual, individual dietary intake of 46 young American women and their husbands, the intake of fat was found to be identical in the 2 sexes.[1] Furthermore, when the salient data available in the literature were analyzed,[1] it became apparent to us that there was no clear-cut evidence to support the belief that the American female might enjoy some sex-linked protection against the supposed *atherogenic* properties of a high-fat diet.

These conclusions led us to consider a second possibility, namely that a high-fat intake *of and by itself* is not specifically responsible either for the greater incidence of *clinical* coronary artery disease in the American male, as compared either to the American female or to men of other races and societies ingesting lower amounts of fat. Again the available experimental and epidemiologic data bearing upon these possible relationships were surveyed.[1, 2] It soon became apparent to us that such data were frequently collected with little or no consideration of such possible important variables as the incidence of hypertension, the striking difference in the incidence of myocardial infarction as opposed to coronary atherosclerosis per se, the qualitative nature of the fats ingested, the means adopted to estimate the actual fat ingestion, changes in incidence of thrombotic accidents, and differences in amount of exercise. Then too, the possible influence of socioeconomic stress was not considered in such epidemiologic studies. Thus Bantus have been compared with American executives, and prosperous yet possibly harrassed Northern Italian merchants and industrialists, with calm Italian peasants of Southern Italy. Yet, despite the obvious social and economic dis-

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parities between such groups, with their possible concomitant effects, only the difference in their fat intake has been accorded a serious relevance to the observed differences in incidence of cardiovascular morbidity and mortality.

The failure of such studies to consider the possible atherogenic influences of socioeconomic stress appears to us to be regrettable if only because, as we earlier have stressed,[1, 2] a better correlation can be obtained between its presence and the incidence of clinical coronary artery disease than between the latter and a high-fat intake.

It was decided therefore to initiate a closely controlled study of the possible effects of one type of socioeconomic stress upon the serum cholesterol and blood coagulation time of a group of intelligent, conscientious male volunteers. The results of this study suggest, we believe, that the factor of socioeconomic stress cannot be disregarded in any future experimental or epidemiologic study dealing with the pathogenesis of clinical coronary artery disease in modern man.

Methods and Material

Selection of a Form of Socioeconomic Stress

In an attempt to discover, hence select a form of socioeconomic stress possibly having a pathogenetic relevance to clinical coronary disease, we interviewed by questionnaire, 162 executives of a large oil company, a railroad company, and 3 advertising agencies. In addition, 47 physicians actually treating cardiac patients were interviewed. Despite the obvious differences existing in the background and training of these lay and professional groups, it was surprising to us that approximately 70 per cent of each group believed that the major cause of *clinical* coronary disease was a particular and rather specific type of emotional activity, namely that concerned with excessive "drive," competition, meeting "deadlines," and economic frustration. Thus both groups sharply differentiated this general form of socioeconomic stress from an anxiety-worry-fear complex, in that only 3 to 5 per cent of either group believed the latter form of emotional perturbation had etiologic significance in the pathogenesis of clinical coronary artery disease. It was of interest too that, despite the recent, widespread dissemination of data purporting to demonstrate a relationship between high-fat intake and coronary artery disease, only 6 per cent of the physicians believed that high-fat intake bore a primary role in the pathogenesis of the disorder under discussion. An even smaller minority blamed inadequate physical exertion.

These results therefore suggested that a form of socioeconomic stress should be selected for study that would impel the subjects to exert "drive," or subject them to a deadline, in short, of imposing upon the subjects a "sense of urgency." Moreover, the application of or exposure to such stress would have to be sufficiently and predictably phasic enough to allow periods of respite for control observations. After considerable study and deliberation, it was decided to study the effects of the type of socioeconomic stress to which certified public, public, and tax accountants are exposed during the first 5 months of the calendar year.

Functional Classification of the Accountants

Forty accountants volunteered for this study which extended for a total period of about 5 months, beginning January 8 and ending on June 10, 1957.

Eighteen of these volunteers (group A) were accountants chiefly concerned with tax returns. These accountants are referred to henceforth as "tax" accountants. It should be pointed out that each of these men was either the owner or a responsible partner of their respective firms. We had been aware from the beginning that only such proprietary individuals in the field of accounting actually experience periods of severe stress. Their average age was 38 years (range 28 to 50 years).

The remaining 22 accountants (group B) specialized in corporate finances. These accountants are referred to henceforth as "corporate" accountants. Again only responsible partner-members of accounting firms were studied. Their average age was 39 years (range 28 to 56 years).

Both groups of accountants made ideal subjects for this study in that they were far above the average in intelligence, sincerity, and finally in their understanding interest in the study itself. At all times, even during their periods of stress, their cooperation was immediate and complete, despite the demands made upon them by the study.

Description of Economic Stress and Lull Periods of the Accountants

Almost all accountants work long hours (as much as 70 hours per week) during the first 4 months of the calendar year, after which time they generally observe much shorter hours (as little as 30 hours per week). However, from our preliminary survey we had been forewarned to gage the intensity of the socioeconomic stress not by the mere number of working hours but rather by the sense of urgency inherent in or engendered by their work activity. By this last criterion, it was

determined that 4 periods of socioeconomic stress (of the type we wished to study) might be encountered by accountants during the first 6 months of the year. For accountants occupying themselves with corporate finances (chiefly certified public accountants), the periods January 1 to 31 and April 1 to 15 were periods of severe stress and that of June 1 to 15 was one of moderate stress. The periods in between these, although possibly demanding long hours, did not carry any sense of urgency. For accountants concerned primarily with tax returns (chiefly public and tax accountants), the period of April 1 to 15 only was one of severe stress and that of March 1 to 15 was one of very mild stress. It should be pointed out that in the majority of the accountants' work, working against a "deadline" is almost inevitable because of the delay in the receipt of all of the clients' data by the accountant. Sometimes indeed these data may become available to him only during the last few days preceding the April 15th or other "deadline."

Recording of Individual Exposures to Other Types of Personal Socioeconomic Stress of the Accountants

The above-mentioned stress periods in the first 5 months of the calendar year of an accountant represented the most intense and harrowing emotional periods for our subjects considered as a whole. Nevertheless, during this same period of time, it was obvious that individual accountants, as the result of various personal experiences and exposures, might incur stresses of similar but far more intense nature than those experienced at the usual critical phases of the accountants' life occurring during the January-June period under study.

Therefore, at the bimonthly visit, each accountant was questioned rather intimately about all forms of emotional perturbation he might have experienced. When such upsets were reported, he was asked to estimate as best he could their relative intensity in comparison with that felt in possible previous similar experiences and also with that noted during the aforementioned general periods of occupational stress to which all accountants were exposed. Thus at the end of the study, we had a complete record of each subject's exposure to various types of personal emotional difficulty, in addition to those specific periods of socioeconomic stress which he showed with all of the other accountants. Finally at the end of the study, we were able to obtain from each subject's review of the past recorded upsets, that one which he considered to have exerted maximal stress of the particular kind we were studying (i.e., socioeconomic stress as defined above). The subjects were asked to give as frank and truthful information as possible during those interviews. From the sometimes delicate and confidential events revealed to us during such interviews, we have good reason to believe that almost without exception, these subjects made every possible attempt to cooperate in this phase of the study.

Recording of Weight and Exercise

Beginning January 8 and continuing biweekly until June 10, 1957, each subject was weighed. He was also questioned at each visit concerning the total number of hours of physical activity indulged in during the past 2 weeks and this was recorded. At the beginning of the study, each accountant was asked to refrain from indulging in any more physical activity during a period of emotional respite than he did during a period of stress. Such a restriction ensured the continued control of this factor, considered by some to play a part in the control of the serum cholesterol level.

Recording of Dietary Intake

From the outset, we were aware of the possible influence of the diet upon the blood chemical values. We also were aware[1] of the total untrustworthiness of any dietary survey that depends upon either the recall abilities of subjects or its calculation from government statistics. We decided therefore to employ the dietary system we had employed in a previous study.[1] Each accountant (after suitable orientation) was given a mimeographed sheet providing space for the *detailed* daily recording for 7 days of his intake of all foods and beverages, both at regular mealtime and otherwise. Each then was asked to record his dietary intake for a period of 1 week, both during a period of maximal occupational stress (April 2 to 9) and again during a period of maximal respite (May 14 to 21).

Recording of Serum Cholesterol and Blood Coagulation Time

Beginning January 8 and continuing biweekly until June 10, 1957, each accountant was bled at 8:00 to 9:00 a.m. and the serum portion of this sample was analyzed for total cholesterol.[3]

Beginning on February 19 and continuing monthly, 19 subjects (13 "tax" and 6 "corporate" accountants) also were bled for determination of their blood coagulation time. Unfortunately, these measurements were not begun until February. Actually we decided to perform this portion of the study only after the fatal coronary thrombosis of one of the accountants in January. For this determination, a 2-tube Lee-White method (2 ml. whole blood per tube) was employed. The time for coagulation was calculated as the average of the time of coagulation of each tube, recorded from the onset of free withdrawal of 5 ml. of blood into a dry syringe through a 21-gage needle. A uniform technic was employed and the coagulation times were determined by the same group of 3 technicians throughout the study period.

TABLE 1.—*Average Daily Dietary Intake*

	Group A		Group B	
	April 2–9	May 14–21	April 2–9	May 14–21
Total calories	1787 (1000–2700)*	1733 (1175–2375)	1895 (1350–2900)	1825 (1300–3200)
Protein (Gm.)	62.6 (40–100)	65.3 (47–80)	66.0 (40–85)	61.0 (50–85)
Carbohyd. (Gm.)	165.0 (85–265)	161.0 (100–210)	181.0 (90–285)	180.0 (150–235)
Fat (Gm.)	86.0 (50–130)	87.6 (70–116)	89.0 (60–140)	83.2 (55–130)
% Dietary fat	43.2 (38.0–49.1)	45.5 (36.4–52.0)	42.2 (36.5–49.7)	41.0 (36.4–48.7)

* Range of values

RESULTS

General Health

Unfortunately, approximately 6 hours after the initial bleeding period on the morning of January 8, 1957, one of the "corporate" accountants (age 48 years) suffered an acute myocardial infarct and died about 2 hours after its clinical onset. At autopsy, a fresh thrombus was found occluding the anterior descending branch of the left coronary artery. This individual, similar to the other "corporate" accountants during the January period, had been under very severe work stress for at least a week prior to this accident. It was of interest that his dentist had communicated to us his amazement at the rapidity with which this man's blood clotted following some therapeutic incisions into his gum tissues the day before his demise.

With this tragic exception, the remaining 39 accountants generally experienced good health throughout the 5-month period. None experienced previously or during the study any cardiorespiratory symptoms.

Weight and Exercise

As figure 1 illustrates, accountants as a group indulge in little physical activity, whether they are in a period of job stress or respite. Furthermore, little real difference was observed in their exercise habits during these same periods. Clearly then, no significant relationship was observed between physical exercise and the presence of socioeconomic stress.

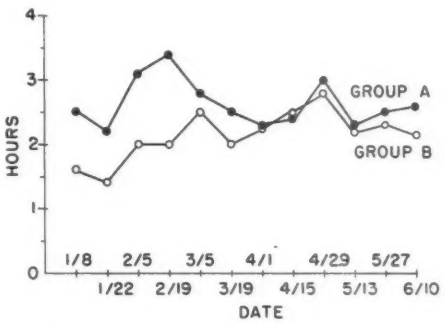


FIG. 1. Average amount of exercise.

Likewise no significant changes in weight were observed in either group of accountants during the period of observation. Actually, in both groups, there were only 3 individuals who gained or lost more than 3 lbs. during the total period of study.

Dietary Intake

The average dietary intakes during the period of April 2 to 9 and also during the period of May 14 to 21 are shown in table 1. As can be seen, during the period of April stress, the dietary intake of calories and of fat of both groups of accountants was quan-

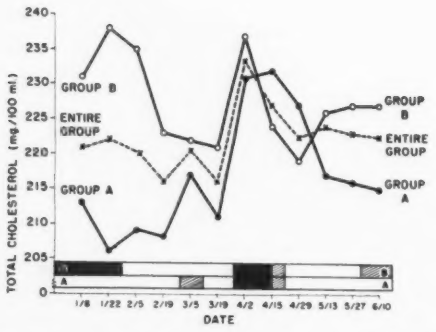


FIG. 2. Serum cholesterol changes observed in 9 representative individual accountants. (Periods of unusually severe work stress are indicated by shaded blocks and periods of severe emotional stress due to other causes by diagonal-lined blocks). (Serum total cholesterol = SC). (*a*) A 47-year-old obese accountant. His SC rose progressively from 269 mg./100 ml. to 325 during a time of severe work stress, then fell to 267 mg./100 ml. and, during the combined stress of the April income tax period and moving his household to a new residence, again rose to 325 mg./100 ml. During the subsequent "lull" in his work, his SC rapidly fell to 251 mg./100 ml. (*b*) A 32-year-old corporation tax specialist whose SC varied between 290 and 305 mg./100 ml. during a period of severe work stress and then rapidly fell to 227 during a subsequent "lull." A progressive rise of SC to 352 mg./100 ml. then occurred during the following period of intense work stress in April. (*c*) This 33-year-old accountant exhibited an SC of 303 to 331 mg./100 ml. during a period of severe emotional tension consequent to severe work stress combined with the emotional strain of studying for the final examinations of his third year of night law school. Subsequently, and in association with administration of Rauwiloid, his SC fell progressively to 224 mg./100 ml. (*d*) A 38-year-old accountant whose SC rose from 230 to 301 mg./100 ml. following a period of unusually heavy work stress during which a child also was hospitalized with an erroneous diagnosis of serious illness. Subsequently his SC fell to 230 to 255 mg./100 ml. (*e*) Age 39. While under severe emotional strain consequent to intense work stress while simultaneously running for local political office, his SC rose from 218 to 269 mg./100 ml. It then rapidly fell to 222, but again rose to 254 mg./100 ml. during the severe stress of the April tax period. Subsequently his SC fell to 194 mg./100 ml. (*f*) The SC of this 37-year-old accountant rose from 190 to 269 mg./100 ml. during a period of unusually heavy work stress in which he also engaged in an unpleasant court "battle" with his estranged wife over child custody. The SC subsequently rapidly fell to 227, but during the severe strain of the April tax period, again rose to 260 mg./100 ml. In the subsequent period of greatly diminished emotional stress his SC fell to 188 mg./100 ml. (*g*) The initial SC observed in this 50-year-old obese accountant was 165 to 170 mg./100 ml. Subsequently, during a time of severe emotional strain occasioned by a heavy work load, his SC rose to 240 mg./100 ml. and, during a time of added stress due to his wife's illness, it rose to 260 mg./100 ml. (*h*) The SC of this 42-year-old accountant varied between 165 and 170 mg./100 ml. during a period of light work, but rose to a peak of 215 mg./100 ml. during a period of severe work stress. (*i*) This extremely obese, 29-year-old accountant exhibited a SC of 184 to 185 mg./100 ml. early in the study period. During a subsequent period of severe work stress in which he became very irritated at his boss, it rose to 220 mg./100 ml. A day after the latter determination he resigned and while on "vacation" his SC fell to 165 mg./100 ml. One week later, at the beginning of the April tax period, he was employed elsewhere, and at this time his SC rose to 216 mg./100 ml. During the subsequent marked "lull" in activity his SC fell progressively to 169 mg./100 ml.

titatively and qualitatively almost identical to that taken during the May period of respite. Again, as was noted in a previous study of *upper class* American males of this same age period,[1] the total number of calories daily ingested was far below that commonly assumed by calculations derived from governmental statistics of "foods available for consumption."

Reactions to Socioeconomic Stress

It was quite obvious to even the casual observer that the subjects of both groups reacted emotionally to their respective periods of economic stress and this without exception. Such reaction revealed itself not only in their frank and candid admissions of a sometimes overpowering sense of urgency, and of the occurrence of irritation, insomnia, nervousness, and even quarrelsomeness with family and colleagues, but also by obvious changes in their demeanor, speech, and general attitude. Such changes clearly confirmed the presence of the phasic emotional strain of the type we wished to study.

Although such reactions were variously observed in all accountants during their respective periods of work stress, certain individual accountants of both groups during the 5-month period experienced 1 or more situations that were considered by them as

more stress-inducing that the usual occupational deadline periods of stress associated with their work. Although most of these additional stressful situations arose again out of business activities, some came from extra-financial activities. Some of these situations and their particular effects are discussed further below.

Serum Cholesterol Changes

Average Group Changes. The changes in the average serum cholesterol concentrations observed in the 2 groups of accountants during the 5-month experimental period are shown in figure 2. Despite the fact that no significant change had occurred in the weight, dietary, or exercise habits of either group, it can be seen that significant changes occurred in the average serum cholesterol of these subjects.

The average cholesterol of the "tax" accountants (group A) varied between 206 and 217 mg. per 100 ml. during their January and February periods of respite but rose during the April stress period to a peak of 232 mg. per 100 ml. on April 15. Subsequently it began to fall, reaching a value of 215 mg. per 100 ml. on June 6. When the ratios of the individual serum cholesterols (average 206 mg. per 100 ml.) obtained on January 22, a period of respite, and those (average 232 mg. per 100 ml.) obtained on April 15, the period of maximal stress, were evaluated statistically, the change in cholesterol was found to be significant ($p < 0.05$).

It was of great interest to us that the "corporate" accountants (group B) who differed from the "tax" accountants in that January was as much or more a period of stress than April, exhibited just as high serum cholesterols during the former period as they did in April (fig. 3). Furthermore, a tendency of the serum cholesterols to rise was observed in June, during which time these accountants again were exposed to moderate stress. Once again however, similar to the "tax" accountants, they had lower serum cholesterol levels during the February and March periods of respite. During these periods however, their average serum cholesterol tended to be somewhat higher than that of the "tax" accountants. Whether this was due to the fact that "corporate" accountants rarely were as free of stress even during periods of time between tax deadlines is a matter of conjecture.

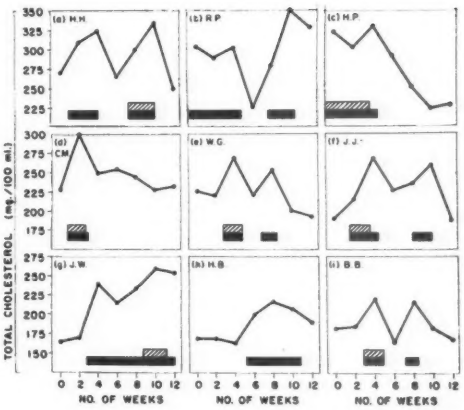


FIG. 3. Average serum cholesterol during experimental interval.

Average Individual Changes. In the preceding section the data indicated that the average serum cholesterol of each group was elevated during the usual and expected periods of severe work stress in the lives of the 2 groups of accountants. However, as was pointed out above, not all of the accountants believed they experienced their maximal emotional reaction to a socioeconomic stress at the usual periods. Thus, for example, one accountant felt, and perhaps rightly, that the stress creating the maximal emotional perturbation in him was not one of the tax deadline periods but a 2-week period in February when he was engaged in a legal battle with his former wife over child custody.

It was considered of interest therefore to compare the average cholesterol of each subject obtained at the time that he considered he experienced his maximum stress with that obtained when he considered his emotional tension to be at its lowest. As can be seen by inspection of table 2, the average serum cholesterol at these times was significantly different. Thus the average serum cholesterol of all accountants was 252 mg. per 100 ml.

TABLE 2.—*Average Serum Cholesterol at Time of Subject's Maximum and Minimum Period of Emotional Stress (All Types)*

Serum cholesterol at time of	Actual range of each subject's serum cholesterol
Maximum stress Average: 252 mg./100 ml. Range: (145–391) S.E. mean: ±7.5	Maximum serum cholesterol 263 mg./100 ml. (160–391) ±8.8
Minimum stress Average: 210 mg./100 ml. Range: (138–354) S.E. mean: ±6.8	Minimum serum cholesterol 200 mg./100 ml. (127–314) ±5.7
Difference Average: 42 Range: (2–125) S.E. Diff. Means: ±10.1	Difference 63 (31–125) ±10.5

at the time they considered themselves under the greatest stress and only 210 mg. per 100 ml. at the time they felt most devoid of tension or a sense of urgency. The difference of the individual cholesterols at these times was statistically highly significant ($p < 0.001$). In conformity with this observed stress-high cholesterol relationship was the fact that the maximum serum cholesterol observed in each individual during the 5-month period occurred in 91 per cent of the subjects at the time of his maximal interval of stress. Conversely, the minimal serum cholesterol occurred in 76 per cent of the subjects at the time of minimal stress. In only 4 instances was there a disparity between the maximal and minimal cholesterol values and respective periods of stress and respite.

It also was of interest that few patients showed a constant serum cholesterol throughout the 5-month period. Actually when the maximal and minimal observed cholesterol values of each subject were obtained and averaged, it was found that they differed by 63 mg. per 100 ml.

Specific Individual Changes. Figure 3 depicts the serum cholesterol variations in 9 of our patients who experienced a stressful situation in addition to the ones to be expected generally in their profession. The rapidity and sometimes the profundity of the rise of serum cholesterol following such unusual stresses are readily apparent, as is its subsequent decline with relief from the stress-inducing event or situation.

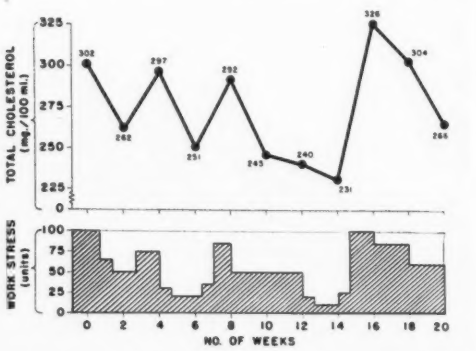
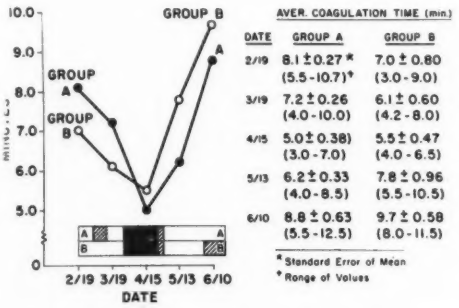


FIG. 4. Correlation of serum cholesterol with accountants' own diary of work stress. When heavily concerned with year-end statements, and while he simultaneously assumed the duties of head of a large corporation when its board chairman suffered a myocardial infarction, his serum cholesterol rose to 302 mg./100 ml., but during a subsequent distinct lull in work activity, it fell to 262 mg./100 ml. With the definite increased stress of a deadline for quarterly tax returns his serum cholesterol again rose to 297 mg./100 ml. and subsequently again fell to 251 during the following period of very light activity. During the ensuing interval of severe work stress preceding the April 15 income tax deadline it again rose, to 292 mg./100 ml. and, during the subsequent marked decrease in work activity, in which time he also took a vacation, his serum cholesterol progressively fell to 231 mg./100 ml. He then entered a period of great emotional tension occasioned by the strain of working on several important and complicated tax problems. At the same time he was successfully competing to have his firm selected to do the accounting for a large Federal project. During this interval his serum cholesterol rose to 326 mg./100 ml., but during the subsequent decrease in his work-load and associated tension, again progressively fell to 266 mg./100 ml.

Unknown to us until the end of the study, one of the accountants (a 43-year-old senior partner of a very busy accounting firm) kept a detailed diary of his work load expressed in his own arbitrary units of 0 to 100. It is believed that this voluntary activity on his part was actuated by his extraordinary



AVER. COAGULATION TIME (min.)

DATE	GROUP A	GROUP B
2/19	8.1 ± 0.27 * (5.5 - 10.7) †	7.0 ± 0.80 (3.0 - 9.0)
3/19	7.2 ± 0.26 (4.0 - 10.0)	6.1 ± 0.60 (4.2 - 8.0)
4/15	5.0 ± 0.38) (3.0 - 7.0)	5.5 ± 0.47 (4.0 - 6.5)
5/13	6.2 ± 0.33 (4.0 - 8.5)	7.8 ± 0.96 (5.5 - 10.5)
6/10	8.8 ± 0.63 (5.5 - 12.5)	9.7 ± 0.58 (8.0 - 11.5)

* Standard Error of Mean
† Range of Values

FIG. 5. Average blood coagulation times.

interest in our project, due in part at least to the fact that he had known for several years that he suffered from xanthelasma and moderate hypercholesteremia. It is of interest that the serum cholesterol values, when placed upon the same graph (fig. 4), exhibited a striking direct relationship to phasic changes in his workload and its associated emotional tension.

Changes in Blood Coagulation. Surprising changes were observed in the blood coagulation time of both groups of accountants at the time of the April period of stress. The marked acceleration of clotting time that occurred in both groups during the April stress period, and its preceding and succeeding return to markedly slower values (fig. 5) during the periods of respite or moderate stress appeared to suggest an inescapable relationship between acceleration of clotting time and the presence of severe socioeconomic stress of the type under investigation. Thus in the February period, the average coagulation times in the subjects of group A and B were 8.1 and 7.0 minutes respectively, and on April 15, they were 5.0 and 5.5 minutes respectively, only to return to 8.8 and 9.7 minutes, respectively, on June 10. Statistical analysis of these changes revealed them to be highly significant ($p < 0.01$).

DISCUSSION

The present studies appear to us to indicate an extreme sensitivity of the serum cholesterol to the occurrence of emotional duress of a particular type herein described as "socioeconomic stress." The possible effects of weight changes, and of dietary and exercise habits of our subjects were followed closely and not found to vary significantly from a period of stress to one of respite; it must therefore be concluded that the stress itself must be accorded primacy in the causation of the observed cholesterol changes. Although inconstancy of the serum cholesterol in serial determinations has been observed previously,[4] particularly in persons with coronary artery disease,[5] only recently has any possible causal relationship been recognized between the occurrence of emotional distress and either a rise or a persistently elevated serum cholesterol.[6, 8] If the exposure to such emotional stress as studied herein can by itself induce these often profound changes in serum cholesterol, then the results of any epidemiologic study of coronary arteriosclerosis predicated upon serum cholesterol differences, not taking this factor into account or confusing it with some other psychiatric entity such as simple anxiety states and psychoneurosis, are indecisive at best. As far as we know however, no epidemiologic study has taken such control precautions. Indeed, the results of most of the reported epidemiologic studies that generally incriminate the high-fat intake of upper middle class Western man as the major cause of their relatively high serum cholesterol could just as well have been utilized to support the concept that socioeconomic stress was the responsible factor.[1] Indeed, it should be noted that various groups exhibiting a relatively low serum cholesterol (e.g., the Bantu, the Japanese peasant, the Southern Italian, etc.) purported by some to be due to a low dietary fat intake, also are not exposed to the type of socioeconomic stress described herein.[1] Moreover, it should also be noted that certain other groups that are free of such particular forms of stress, exhibit similarly low serum cholesterols despite a high-fat intake.[1, 2] Finally, it should not be forgotten that Bronte-Stewart et al.[9] remarked in their South African studies that if "job responsi-

bility'' were employed as an indicator of stress, as good a correlation could be found between its variations and the varying incidence of clinical coronary disease in their subjects as that which they believed existed between the dietary fat intake and the latter.

The finding of a markedly accelerated clotting time in our subjects at the time of severe occupational stress appears as a possibly more important phenomenon than the elevation of their plasma cholesterol. When it is remembered that there has not been a significant *increase* in the serum cholesterol or dietary fat intake[10, 11] or in either the incidence or severity of coronary atherosclerosis per se[12–14] in Western men, but only in the incidence of coronary thrombosis[15–17] during the past 5 decades, the reason for this viewpoint becomes understandable.

Summary

Serum cholesterol was obtained biweekly and blood coagulation time at monthly intervals from 40 volunteer accountants during the first 5 months of 1957, in order to study the effects of socioeconomic stress upon these 2 factors. Members of the accounting profession were selected for this study because of the sudden and marked phasic variations in their work stress uniquely imposed by the several ''deadlines'' in the tax calendar. The results indicate that severe occupational stress or other forms of unusual emotional tension are associated both with a sudden and often profound rise of serum cholesterol and a marked acceleration of blood coagulation time. The possible causal relationship of occupational and other socioeconomic stress both to coronary atherosclerosis and thrombosis is discussed briefly.

Acknowledgment

The authors wish to thank Frances Dahl, Dietitian, for analyses of the diet sheets.

Summario in Interlingua

Le valores del cholesterol seral esseva determinate a intervallos de duo septimanas e le tempore del coagulation de sanguine a intervallos mensual in 40 voluntarios cuje occupation esseva le contabilitate. Le studio esseva continuate durante le prime 5 menses del anno 1957. Su objectivo esseva determinar le influentia de stresses socio-economic super le 2 factores mentionate. Contabiles esseva seligite pro iste studio a causa del subite e marcate variationes phasic in le stress de lor labor que depende rigorosemente del varie ''datas terminal'' in le calendario del taxation. Le resultatos del studio indica que sever stresses occupational o altere formas de inusual tension emotional es associate con un subite e frequentemente marcate augmento del cholesterol seral e etiam con un acceleration considerabile del coagulation del sanguine. Es presentate un breve discussion del possibile relation causal de stresses occupational e alteremente socio-economic con atherosclerosis coronari e con thrombosis coronari.

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Medical Eponyms

By Robert W. Buck, M.D.

Grocco's Triangle. Professor Pietro Grocco (1857-1916) of Florence first described his triangle at the fourth session of the Twelfth Congress of the *Societa Italiana di Medicina Interna* in October, 1902. An abstract of his remarks appears under the title "The Paravertebral Triangle on the Side Opposite to Pleurisy with Effusion" (*Triangolo Paravertebrale Opposto Nella Pleurite essudativa*) in the transactions of the society: *Lavori dei Congresso di Medicina Interna* **12**: 190, 1902 (Rome, 1903).

"Professor Grocco thus designates a new symptom which he has often found in pleurisy with effusion. It consists in a triangular area of relative dulness on the posterior wall of the thorax opposite to the side involved. The internal border of this triangle is represented by the line of the spinous processes, the base by the lower limit of thoracic resonance (which varies somewhat over a space of 3 to 6 cm.), and the external border by a line which extends obliquely upward to the highest point reached by the level of the exudate. Over this area the impairment of sound is more marked toward the median line and toward the base, and the base line itself varies in length and degree of dulness with different positions of the patient as he lies in bed, and with variations in the amount of fluid. The fluoroscope and radiogram confirm the percussion findings. This is illustrated by the accompanying figure, which shows two radiograms, one taken during life, the other from a cadaver in which one pleural cavity was filled with a solution of lead acetate. The test on the cadaver tends to support the idea that the pleural sac, when full of fluid, extends beyond the median line sufficiently and in such a way as to explain the triangle area of dulness above mentioned."

Regression after Open Valvotomy of Infundibular Stenosis Accompanying Severe Valvular Pulmonic Stenosis

By Mary Allen Engle, M.D., George R. Holswade, M.D., Henry P. Goldberg, M.D., Daniel S. Lukas, M.D., and Frank Glenn, M.D.

Three patients operated upon under hypothermia for severe valvular pulmonic stenosis had right ventricular pressures in excess of 100 mm. Hg after open valvotomy. The residual obstruction, localized by pressure measurements to the subvalvular region, appeared to be due to greatly hypertrophied musculature in the outflow tract of the ventricle. Infundibular resection was not attempted. Electrocardiographic signs of right ventricular hypertrophy gradually disappeared, and cardiac catheterization about 1 year after surgery showed normal or nearly normal right ventricular pressures. Postoperative improvement is attributed to regression of hypertrophy of the right ventricle consequent to relief of obstruction at the valve.

OPEN pulmonary valvotomy through the pulmonary artery in the hypothermic patient was adopted at The New York Hospital in January 1956, because the relief of valvular stenosis afforded by this technic was reported to be more complete than by closed methods.[1-3] It was anticipated that correction of the stenosis by an adequate valvotomy would be evidenced in the operating room by a prompt reduction of right ventricular pressure to nearly normal levels. However, within the first year of experience with this operation, 3 patients with severe valvular pulmonic stenosis and intact cardiac septa were encountered who still had a right ventricular pressure in excess of 100 mm. Hg after completion of the procedure. An area of obstruction to pulmonary blood flow remained which, by pressure measurements obtained by needle puncture through the ventricular wall, was localized to the subvalvular portion of the right ventricle.

When this situation was first encountered, we were confronted with a difficult decision. To open the right ventricle and resect the obstructing tissue was deemed unwise, because of the risk of inducing uncontrollable ventricular fibrillation in the hypothermic heart. But to do nothing further and leave the patient with an obstruction sufficient to produce a right ventricular pressure greater than 100 mm. Hg also caused us concern. There seemed to be less risk in the second choice; so it was decided to see how much benefit would be derived from relief of the stenosis at the pulmonary valve. Should additional surgery on the infundibular area be necessary, it could be done with the aid of extracorporeal circulation. There was hope that this obstruction was due to hypertrophied musculature that would decrease in size after valvotomy lessened the work load on the right ventricle; but there was little evidence at the time to indicate such a fortunate outcome ever happened.

Observations on these 3 patients are reported below. The pressure measurements are summarized in table 1. Cardiac catheterization was performed within the few weeks preceding operation and from 10 to 15 months after valvotomy. In the operating room pressures were measured through direct needle puncture of the right ventricle and pulmonary artery with a Statham P23D strain-gage transducer and were recorded on a Sanborn Poly-Viso recorder. Measurements were obtained immediately preceding circulatory occlusion. They were again recorded after valvotomy and

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TABLE 1.—*Changes in Right-Sided Pressures (mm. Hg) before and after Valvotomy*

Patient	Age (yrs.)	Preoperative catheterization (time)		Operating room		Postoperative catherization (time)
				Before valvotomy	After valvotomy	
E.L.	5 6/12	(8 d.)	*RV* 178/7	170/0	125/0	29/4 (14 mo.)
			PA 16/7	15/5	36/6	23/4
E.R.	27	(2 wk.)	*RV* 158/8	160/5	155/10	20/6 (15 mo.)
			PA 12/5	20/10	20/10	21/5
B.R.	1 9/12	(2 mo.)	*RV* 162/3	175/15	100/20	35/6 (10 mo.)
			PA ——	23/13	31/16	20/4

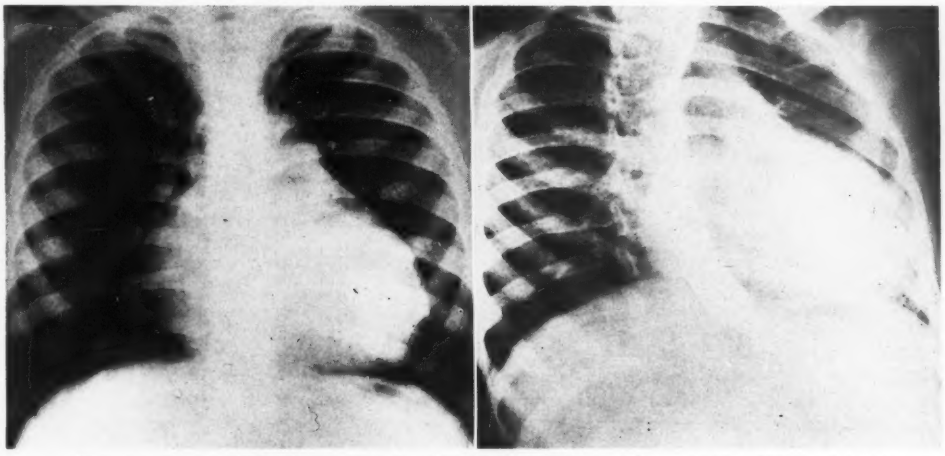

FIG. 1. Case 1. Roentgenograms in frontal (*left*) and right anterior oblique (*right*) projections show cardiac enlargement, in particular of the right atrium and right ventricle, and absence of poststenotic dilatation of main pulmonary artery. Peripheral lung fields hypovascular. *(Reprinted with permission from Pediatrics* 19: *1144, 1957.)*

infundibular exploration, when the circulation had been restored, the incision in the pulmonary artery sutured, and the electrocardiogram, pulse rate, and systemic blood pressure had returned to pre-occlusion levels.

CASE REPORTS

Case 1. E. L., 563942, was 5½ years old at the time of surgery.[4] She was born prematurely at The New York Hospital in 1950, after a pregnancy complicated by exposure of the mother to German measles during the second month. A twin was macerated. A systolic murmur was detected at birth, and there was cardiac enlargement. For the first 3 months the baby was cyanotic. She then did well until about 4 years of age when she could not keep up with other children at play. The heart enlarged progressively to a cardiothoracic ratio of 59 per cent (fig. 1), and electrocardiograms showed progressively more marked right ventricular hypertrophy with the development at age 5 of right ventricular "strain." She was acyanotic, but had a left parasternal bulge and a systolic thrill and murmur in the pulmonary area. The pulmonary component of the second heart sound was diminished.

The findings were those of severe valvular pulmonic stenosis with intact cardiac septa. However, 2 features raised the question of accompanying infundibular stenosis: first, the wide radiation of the systolic murmur along the left sternal border from the first through the fourth interspaces and second, the absence of much poststenotic dilatation of the main pulmonary artery (fig. 1).

At cardiac catheterization (table 1) the pressure changed abruptly at the level of the pulmonary valve from 16/7 mm. Hg in the pulmonary

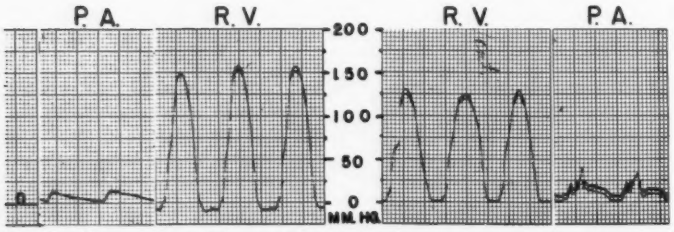

FIG. 2. Case 1. Pressures in right ventricle and pulmonary artery taken in operating room before (*left*) and after (*right*) valvotomy.

artery to 178/7 mm. in the right ventricle. No shunt was demonstrable in either direction.

A week later, on January 20, 1956, the patient was cooled to 29 C. and pulmonary valvotomy was performed under direct vision. Right ventricular and pulmonary arterial pressures measured prior to interruption of the circulation agreed closely with those at cardiac catheterization. A small, cone-shaped valve with an orifice approximately 2 mm. in diameter was grasped and incised to the valve ring. To our surprise, the pressures measured after restoration and stabilization of the circulation showed only a partial reduction of the right ventricular pressure to 125/0 mm. Hg (fig. 2). Pressures recorded at different levels of the right ventricle were consistently elevated but in the distal portion of the outflow tract, just proximal to the pulmonic valve, the pressure was 40/6, a few mm. higher than that in the pulmonary artery. The muscle here was unusually thick, judged by the depth to which the needle had to be introduced to record a cavity pressure. It was believed that the valvular stenosis had been relieved but that there was co-existent subvalvular stenosis. Ventriculotomy and infundibular resection under hypothermia were considered contraindicated.

The postoperative course was one of steady improvement to the point of unlimited exercise without symptoms. During the first 6 months the electrocardiographic evidence of right ventricular "strain" disappeared and the pattern of right ventricular hypertrophy regressed, to be replaced by an rsR′ complex of normal amplitude in the right precordial leads[4] (fig. 3).

Cardiac catheterization 14 months after the operation demonstrated a slight gradient of only 6 mm. Hg across the pulmonic valve, but the right ventricular pressure was normal. With exercise the gradient during systole increased to 14 mm. There was no shunt, and the cardiac output was normal (table 1).

Case 2. E. R., 237581, was operated upon at the age of 27 years. She was first seen at the New York Hospital when 10 years old because of a heart murmur known since the age of 1 year. Ordinary activity produced no symptoms, but she became fatigued and short of breath with strenuous exercise. There was a loud, harsh systolic murmur maximal in the pulmonary area. The heart was not enlarged. The 3-lead electrocardiogram showed right axis deviation with abnormally large amplitude of S_1 and R_3 deflections, indicative of right ventricular hypertrophy. By the age of 13, changes in the T waves that are associated with right ventricular "strain" (deeply inverted T_3 and biphasic T_2) were present.

After adolescence she continued to live comfortably within the restricted activities advised by physicians. She did not return to the hospital until age 27, this time because of infertility since her marriage 6½ years earlier.

Her blood pressure was 120/70 and the pulse was 80. She was not cyanotic, and there was no clubbing. Cardiac findings included a slight left parasternal bulge, a coarse systolic thrill, and a long, loud, harsh systolic murmur maximal in the first and second interspaces and audible over the precordium, in the neck vessels, and the lung fields. The pulmonic component of the second heart sound at the base was inaudible. Diastole was clear. The neck veins were flat, and the liver was not enlarged or pulsatile. Peripheral pulses were normal.

Roentgenograms and fluoroscopy of the chest in frontal and oblique projections showed a cardiothoracic ratio of 45 per cent and slight enlargement of the right ventricle. There was normal prominence of the main pulmonary artery (fig. 4). Pulsations were diminished in the branches, and pulmonary vascularity in the peripheral lung fields was slightly decreased. An electrocardiogram showed right ventricular hypertrophy and "strain" with T-wave abnormalities more marked than at age 13. The blood count was normal.

The impression was severe valvular pulmonic stenosis with intact cardiac septa. The absence of poststenotic dilatation of the main pulmonary artery raised the question of accompanying infundibular stenosis.

At cardiac catheterization the pressure change from a pulmonary artery pressure of 12/5 mm. to a right ventricular pressure of 158/8 mm. Hg occurred abruptly at the valvular region on re-

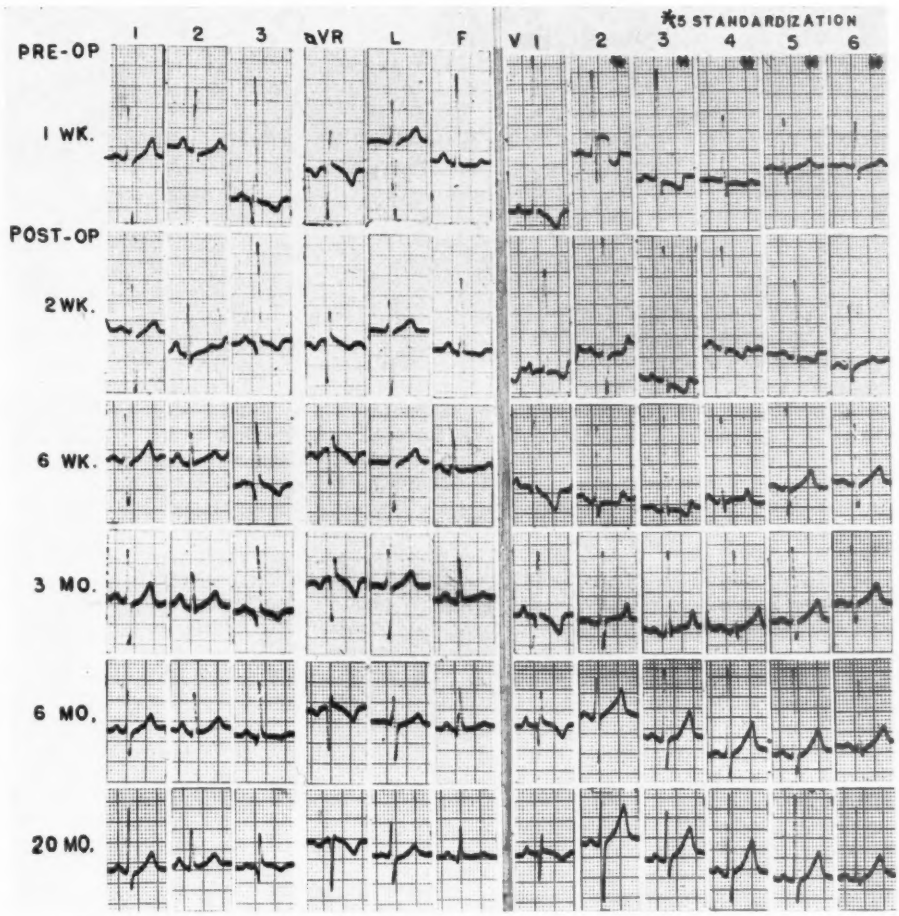

FIG. 3. Case 1. Regression of electrocardiographic evidence of right ventricular hypertrophy and "strain" in limb leads (*left*) and precordial leads (*right*).

peated withdrawals of the catheter (fig. 5). On exercise the right ventricular pressure rose to 195/11 mm. of Hg. Thus catheterization studies supported the diagnosis of severe isolated valvular pulmonic stenosis.

Pulmonary valvotomy was performed under direct vision on June 15, 1956, with the patient's temperature reduced to 28 C. Pressures measured in the right ventricle and pulmonary artery prior to occlusion of the circulation were in agreement with the readings obtained at catheterization. During 3½ minutes of circulatory occlusion the pulmonary artery was opened, and a cone-shaped, fused pulmonic valve with an orifice about 2 mm. in diameter was incised on each side out to the valve ring. The surgeon introduced his finger through the opened valve into the right ventricle and noted some narrowing of the outlet of the ventricle.

After the occluding tapes were released and regular sinus rhythm and systolic blood pressure had stabilized at the pre-occlusion values, pressures were again measured and found to be unchanged. It was thought that 2 incisions in what should normally be a 3-cusped pulmonic valve might have been inadequate. Therefore, the circulation was occluded for an additional 3½ minutes while the pulmonary valve and infundibular region were re-explored. The pulmonary valve was seen to be opened fully to the valve ring; nevertheless, another incision was made in it. The surgeon was convinced that it was opened to its fullest extent. Visual and digital inspection of the right ventricle indicated that there was a marked narrowing of the

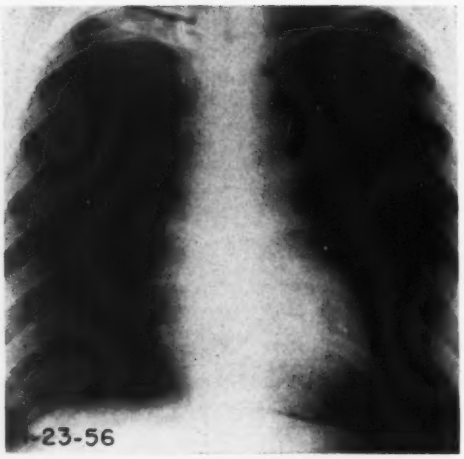

FIG. 4. Case 2. Roentgenogram shows clear peripheral lung fields and absence of dilatation of main pulmonary artery. Cardiothoracic ratio is 45 per cent.

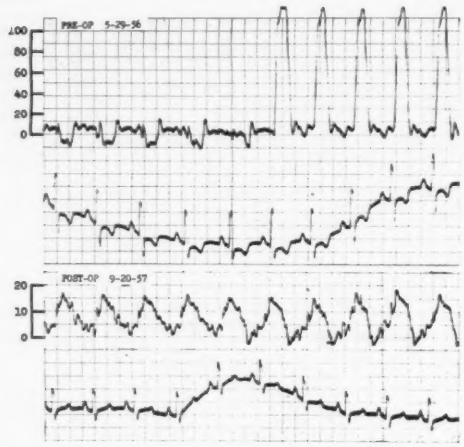

FIG. 5. Case 2. Pressure tracings on withdrawal of catheter from pulmonary artery into right ventricle. Preoperatively (*top*) there is an abrupt rise in pressure as the region of the pulmonary valve is passed. Fifteen months after surgery (*bottom*) there are normal pressures and no systolic gradient.

outflow portion. During diastole the finger could readily be inserted, but this area contracted tightly about the finger during systole. When the finger was removed, the subvalvular portion of the ventricle could be seen to open and then to close tightly like a sphincter with each contraction of the heart.

After the circulation was restored and the incision in the pulmonary artery was closed, a third set of pressure readings was obtained. They differed very little from the prevalvotomy determinations (fig. 6). Pressure in the right ventricle just below the pulmonic valve ring was similar to that in the pulmonary artery.

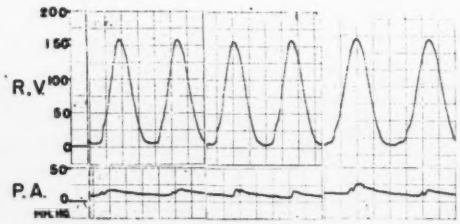

FIG. 6. Case 2. Pressures measured in operating room before (*left*) and after first (*middle*) and second (*right*) valvotomies show persistence of high pressure in right ventricle.

The postoperative course was complicated by a delayed febrile reaction with chest pain and pleural and pericardial effusions, interpreted as the postpericardiotomy syndrome.[5]

Within the next 6 months the patient was able to exercise normally and vigorously without fatigue or dyspnea. She now realized the limitations she had minimized preoperatively. By the sixth month the electrocardiographic pattern of the right ventricular "strain" and hypertrophy had disappeared. Instead, there was normal left ventricular dominance and an rsR′ pattern in V_{3R} and V_1; the amplitude of the deflections was normal (fig. 7). Her heart size was normal, the second sound in the pulmonic area was easily heard, and at the left base there was a soft systolic murmur followed by a short, soft diastolic murmur of pulmonary insufficiency.

By this time she was 3 months' pregnant and on the first anniversary of her operation she gave birth to a healthy girl. She tolerated the pregnancy and delivery without difficulty.

Three months later cardiac catheterization was repeated. The cardiac output, previously restricted, was greater than normal and the pressures were normal. The systolic gradient between the right ventricle and pulmonary artery had been completely abolished (fig. 5 and table 1).

Case 3. B. R., 740274, was an infant 21 months old at the time of valvotomy. She fatigued somewhat more quickly than others of her age but otherwise seemed healthy.

She was normal in size and showed neither cyanosis, clubbing, nor chest deformity. A systolic thrill was palpable over the pulmonary area and a harsh systolic murmur was maximal there. It was transmitted over the heart to the lung fields and to the neck. The second heart sound was

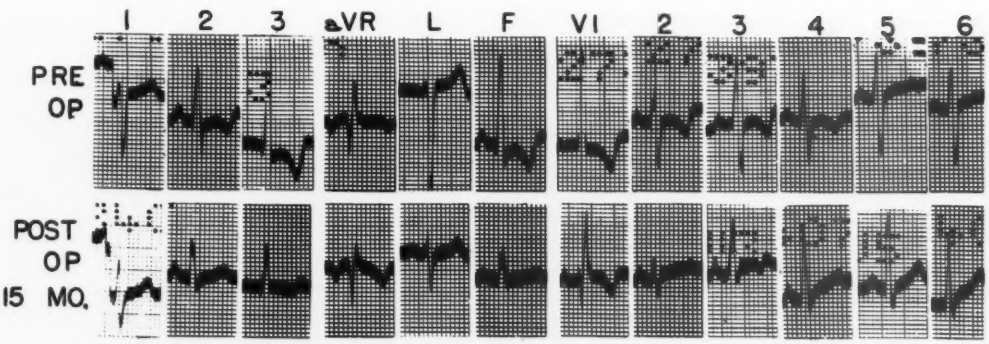

FIG. 7. Case 2. Preoperative and postoperative electrocardiograms show regression of right ventricular hypertrophy and "strain."

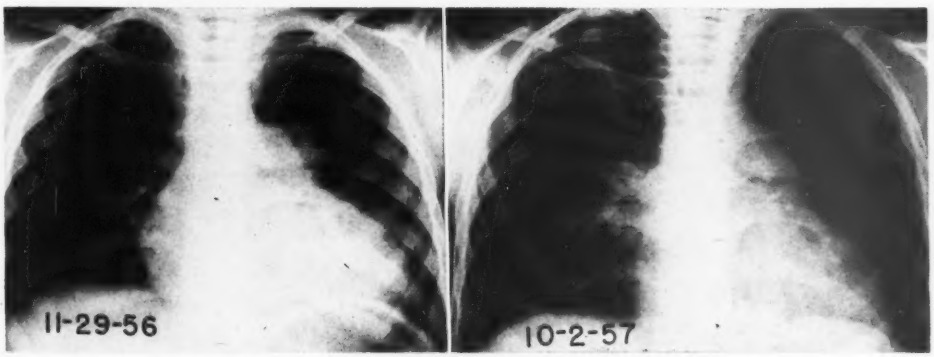

FIG. 8. Case 3. Roentgenograms of chest. *Left.* Preoperatively there is cardiac enlargement with poststenotic dilatation of main pulmonary artery and excessively clear peripheral lung fields. *Right.* Postoperative decrease in heart size. Marked convexity of main pulmonary artery remains.

diminished at the left base. There was no venous distention. and the liver was not palpable.

Fluoroscopy and roentgenograms of the chest disclosed a cardiothoracic ratio of 59 per cent with enlargement of the right atrium, right ventricle, and main pulmonary artery. The peripheral lung fields were excessively clear (fig. 8). An electrocardiogram showed right atrial enlargement, right ventricular hypertrophy, and "strain." Blood counts were normal.

The impression was that she had severe valvular pulmonic stenosis with intact cardiac septa. Despite the few symptoms surgery was advised because of the radiologic and electrocardiographic evidence of severe pulmonary stenosis. Preoperative cardiac catheterization (table 1) recorded a right ventricular hypertension of 162/3 mm. Hg. The catheter tip could not be advanced through the pulmonary valve into the pulmonary artery. No shunt was demonstrable. The arterial oxyhemoglobin saturation was 95.6 per cent.

Operation on the pulmonary valve under direct vision was performed on November 30, 1956. Pressures in the operating room prior to circulatory occlusion at a temperature of 28 C. measured 175/15 in the right ventricle and 23/18 mm. Hg in the pulmonary artery. Three incisions were made in the stenotic valve out to the valve ring. A clamp passed through the valve into the right ventricle met no fixed obstruction when it was spread. The circulation was interrupted for 4½ minutes. After the incision in the pulmonary artery was sutured and the heart rate and systemic blood pressure had returned to their previous levels, pressures were again measured. A somewhat damped right ventricular tracing showed a pressure of 100/20 mm. Hg in the right ventricle and a reading of 31/16 in the pulmonary artery. Though there remained a high pressure in the right ventricle, no additional procedures were undertaken because the valvular stenosis was considered relieved and because by this time the marked postoperative improvement in the first patient had become evident.

She too showed progressive improvement in the

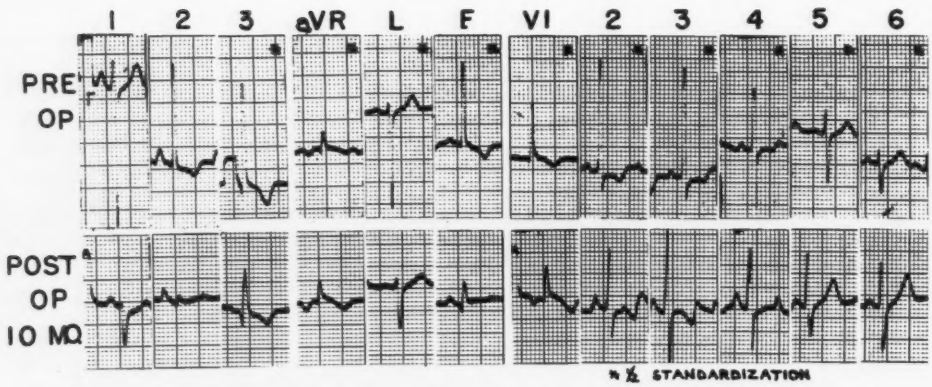

FIG. 9. Case 3. Electrocardiograms before and 10 months after surgery show marked improvement in evidence of right atrial enlargement and right ventricular hypertrophy and "strain."

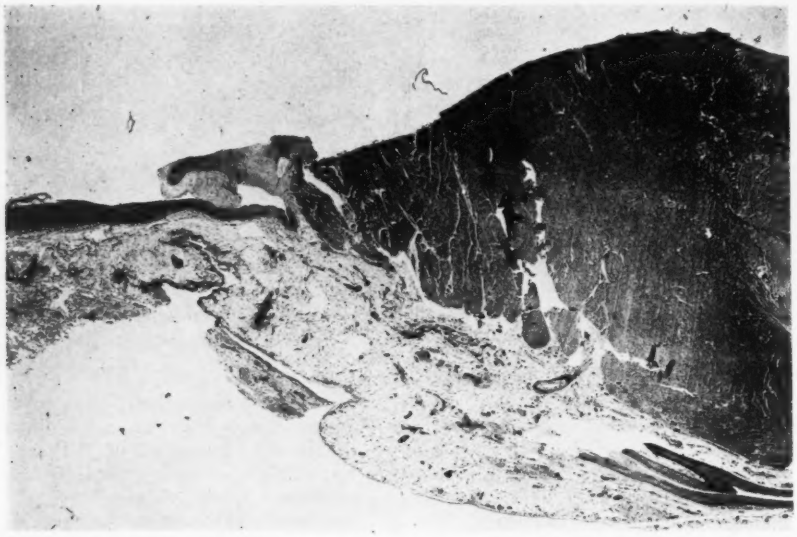

FIG. 10. Section through pulmonary artery, pulmonary valve, and right ventricle of 5-year-old child with severe valvular pulmonic stenosis and intact ventricular septum. Note bulge of thick muscular wall beneath the valve.

electrocardiogram, with regression of right ventricular "strain" and hypertrophy and the appearance of an rsR′ pattern over the right ventricle (fig. 9). The heart size decreased (fig. 8). Cardiac catheterization performed 10 months postoperatively revealed a nearly normal pressure in the right ventricle of 35/6 and in the pulmonary artery of 20/4 mm. Hg (table 1).

DISCUSSION

This form of infundibular pulmonic stenosis accompanying severe valvular pulmonic stenosis is attributed to the marked hypertrophy of the right ventricular musculature. The great muscular thickening of the wall of the right ventricle that is found in patients with extreme valvular pulmonic stenosis and intact ventricular septum is well known. The manner in which the muscle mass bulges beneath the fused valve leaflets is illustrated in figure 10 by a section made through the pulmonary artery, pulmonary valve, and adja-

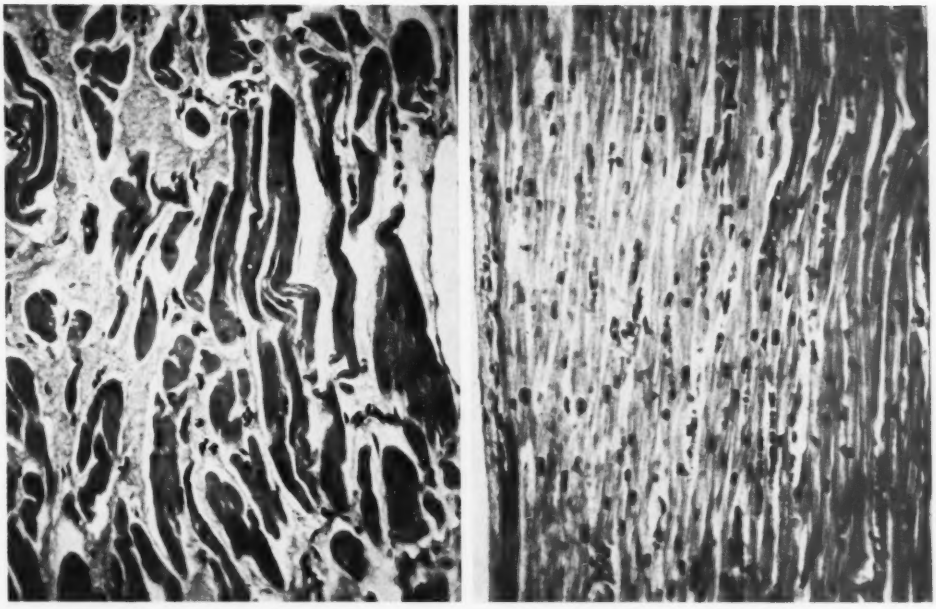

FIG. 11. *Left.* Magnification (300×) of section through right ventricle shown in figure 10. Note tremendous hypertrophy of myocardial fibers and intercellular fibrosis. *Right.* Section through left ventricle of child of same age without heart disease is shown at same magnification for comparison.

cent right ventricle of a 5-year-old boy who died in heart failure from this congenital anomaly. The tremendously hypertrophied muscle fibers and fibrous tissue in this region are shown in figure 11.

In addition to the uniform hypertrophy of the wall of the right ventricle, there are 2 muscle bundles in the infundibulum that are particularly enlarged in this malformation. Both Brock[6] and Kirklin and associates[7] have called attention to the importance of these bands in narrowing the outflow tract of the right ventricle. One, the crista supraventricularis, extends from the pulmonary valve down to the anterior wall of the right ventricle. The other bundle, composed of parietal and septal bands, extends from the pulmonary valve down along the ventricular septum.

The thickening of the muscle wall and of these bundles was sufficient to produce significant narrowing of the outflow tract in 4 of 6 specimens of marked pulmonic stenosis with intact ventricular septum reviewed by Kirklin.[7] This was true also in 6 specimens with this malformation available for re-examination from the autopsy files at the New York Hospital. These 6 patients died as a result of severe valvular pulmonic stenosis at the ages of 7 and 15 days, and 2, 4½, 5½, and 30 years.

To evaluate obstruction of the subpulmonary tract, Bing and his co-workers[8] made a paraffin cast of the cardiac chambers and pulmonary artery of a man who died with pulmonic stenosis and atrial septal defect. They stated that although muscular hypertrophy may exist in this condition, it did not result in narrowing of the right ventricular outflow tract. We believe it may have been the inability to evaluate by this technic the dynamic role of muscular contraction that led to their opinion.

It is difficult to apply to the living patient the information obtained from postmortem specimens. Though these indicate co-existent

infundibular narrowing in some patients with marked valvular stenosis, a better estimate of the situation during life may be obtained by visualization of this region during systole and diastole. Angiocardiographic studies by Kjellberg and co-workers[9] and by Campeti[10] did not show a fixed infundibular obstruction in patients with valvular pulmonic stenosis. These pictures showed no constriction early in systole, but they graphically portrayed the narrowing imparted to this region at the end of systole by forceful contraction of the crista supraventricularis, hypertrophied muscle bands, and ventricular wall.

Rodbard et al.[11] described pressure changes at cardiac catheterization in 10 patients in whom he postulated that muscular contraction in the infundibular region served as a mechanism of pulmonic stenosis. He demonstrated the development of a gradient between the ventricle and the pulmonary artery that was greater in late than in early systole. In one of these patients a muscular ring was found at surgery.

Exaggeration of the infundibular narrowing by myocardial contraction was appreciated in case 2 of this report by the surgeon as he felt the muscle tighten about his finger. On withdrawal of the finger, the subvalvular portion of the ventricle could be seen to close like a sphincter.

Of interest in regard to infundibular muscular hypertrophy as a mechanism of obstruction of pulmonary blood flow is the description by Gasul and his co-workers[12] of the development of infundibular stenosis in infants with ventricular septal defect. They had increased pulmonary blood flow and no evidence of pulmonary stenosis on first catheterization. Though the mechanism responsible for this development is probably different, similar anatomic and functional changes may occur in the outflow tract of the right ventricle in these 2 situations, one with increased and the other with impeded pulmonary flow.

The size of the pulmonary valve ring may also contribute to the obstruction to pulmonary blood flow that was found after valvotomy. This is difficult to evaluate because no measurements of the valve ring were made in the 3 patients, though the area appeared smaller than normal. Less attention has been paid in the literature to the circumference of the valve ring in this anomaly than to the size of the opening in the fused cusps. However, there are a number of reports in which the ring of the pulmonary valve was found to be small when the stenosis of the valve was marked. For example, Ordway et al.[13] found the circumference of the pulmonary valve ring to be 4 cm. in a 25-year-old man whose aortic ring measured 6 cm. The central opening in the stenosed pulmonary valve was 2.5 mm. in diameter. The pulmonic valve ring of a 39-year-old man reported by Selzer and collaborators[14] measured 5 cm. in circumference, in comparison to the aortic ring, 7.2 cm. The tiny orifice in the pulmonary cone was 2 mm. across. One of the specimens reviewed by us was that of a 30-year-old woman, whose pulmonary valve was 4.5 cm. and aortic valve 8 cm. in circumference. The diameter of the opening in the diaphragm-like pulmonary valve was 2 mm. According to Saphir[15] the circumferences in the normal adult are 8.5 cm. for the pulmonic and 7.5 cm. for the aortic valve.

Calculations of the pressure-flow relationships across a valve of this limited circumference indicate that the area enclosed by the ring is not small enough to cause more than a mild obstruction. It is possible, however, that the slight systolic pressure gradient observed at postoperative catheterization in patients 1 and 3 may have been due to a smaller valve ring than is normal.

In our 3 patients, it is puzzling why only 1 area of stenosis was detected by preoperative cardiac catheterization if 2 areas were found to exist at operation. In case 2, repeated withdrawals of the catheter from pulmonary artery to right ventricle gave a sharp pressure change at the region of the pulmonary valve, with no indication of an intermediate zone (fig. 5). In case 1, a few ven-

ricular premature beats occurred as the catheter entered the ventricle from the pulmonary artery, so that the pressures for these few beats were more difficult to evaluate. Nonetheless, the change to a high pressure seemed to take place at the level of the valve. In the third patient, the tip of the catheter appeared to hang in the region of a pulmonary valve. The probable explanation for the paradoxical appearance of a second area of obstruction after valvotomy was suggested by Brock.[6] When the valve was intact, he thought that the high pressure in the ventricle distended the chamber so that the thick muscular walls of the infundibulum were held apart. Relief of the obstruction at the valve might lower the pressure enough for the walls to come together and produce a subvalvular stenosis with hypertension proximal to the block.

Although this explanation indicates that the infundibular stenosis becomes significant after valvotomy, it is of interest that clinically 2 patients (E. L. and E. R.) had features that preoperatively suggested associated infundibular stenosis: absence of poststenotic dilatation so common in valvular pulmonary stenosis, and in the first child, wide radiation of the systolic murmur along the left sternal border rather than maximal localization in the second interspace.

Cineangiocardiography or selective angiocardiography with frequent exposures correlated with the electrocardiogram might help in the preoperative distinction between a fixed subvalvular obstruction, rigid during all phases of the cardiac cycle, and one due to contraction of thick muscle.[9, 10]

One may speculate on the reason for continued improvement in these patients who were left with an important area of obstruction proximal to the one that was relieved surgically. The work of the heart was lessened by the decreased resistance at the valve. Decrease in size of the muscle fibers, in response to the decreased work, would cause less and less obstruction during infundibular contraction. Thus there would be progressively decreasing work and concomitantly increasing lumen in the outflow tract of the ventricle as the thick muscle mass melted away. Electrocardiographic evidence indicated that most of this regression of hypertrophy took place in the first 6 months after surgery but continued even up to 20 months.

Preliminary observations on regression of hypertrophy in the first patient were published in June 1957.[4] One month later Himmelstein and his co-workers[16] reported a patient, aged 14, in whom they believed there had been some reduction in hypertrophy of the musculature of the right ventricular outflow tract following closed transventricular valvotomy. The pressure in the right ventricle was reduced at operation from 180/5 to 130/5 mm., but 6 months after operation the pressure had fallen to 60/7 mm. She too was said to show a decrease in electrocardiographic evidence of right ventricular hypertrophy.

Regression after valvotomy of accompanying infundibular stenosis may have occurred in a patient reported by Kirklin and in one by Campbell and Brock. Kirklin and associates[7] reported a patient in whom cardiac catheterization studies 5 months after a closed pulmonary valvotomy showed a fall in right ventricular pressure, despite persistence of subvalvular stenosis after operation. Right ventricular pressure was 125/5 before and 110/5 mm. after valvotomy. Five months later it was 65/8 mm. of Hg. In this patient, as well as Himmelstein's, studies later than the sixth postoperative month might have shown even a more striking reduction in right ventricular hypertension.

Case V78 reported by Campbell and Brock in 1955[2] showed an improvement in right ventricular pressure at postoperative cardiac catheterization that was not evident immediately following a closed valvotomy. Right ventricular pressures in the operating room were 97/5 before and 94/9 mm. after valvotomy. Catheterization at an unspecified time after operation revealed a pressure of 31/0 in the right ventricle and 19/6 mm. in the pulmonary artery.

Manning and Mahoney[17] have recently

studied 3 patients similar to ours who showed regression of infundibular stenosis following open pulmonary valvotomy. A report on their observations is in progress.

We believe that open valvotomy has an advantage over closed procedures when this situation is encountered in the operating room. The surgeon can then be confident that the stenosis at the valve has been completely relieved. Repeated manipulations of the valve are unnecessary. Inspection of the subvalvular region can then be carried out by direct vision into the empty heart, by finger palpation, or by the introduction of an instrument that can be spread open inside the chamber. If no fixed, rigid infundibular obstruction, such as a diaphragm or ring is encountered, then experience from these 3 patients implies that no further surgical procedures are indicated. Though infundibular resection has been recommended if a significant systolic gradient remains after valvotomy, we believe that the type of infundibular stenosis due to muscular hypertrophy is better and more safely treated by giving it the opportunity to regress after valvotomy.

Summary and Conclusions

Three patients, an infant, a child, and an adult, with severe valvular stenosis were observed to have a right ventricular systolic pressure greater than 100 mm. Hg following valvotomy performed under hypothermia through an opening in the pulmonary artery. The obstruction that remained was localized by pressure measurements to the outflow tract of the ventricle. Intracardiac exploration of this region indicated that the obstruction was not rigid but appeared to be due to contraction of the hypertrophied muscle. During 6 to 20 months postoperatively electrocardiographic signs of right ventricular hypertrophy disappeared, and cardiac catheterization 10 to 15 months after operation disclosed pressures within normal limits in the right ventricle with only slight or no transvalvular gradients.

It appeared that the severe valvular stenosis was responsible for marked hypertrophy of the wall of the right ventricle, sufficient by itself to narrow the outflow tract once the obstruction at the valve was relieved. Restoration of valve function by valvoplasty reduced the work of the ventricle so that the hypertrophied myocardial fibers returned to a more nearly normal size and was accompanied by complete regression of this secondary form of infundibular stenosis.

The surgical implication from these observations is that if the valve has been opened fully and no fixed obstruction, such as a diaphragm or ring, is found within the right ventricle, then additional attempts to treat the muscular stenosis surgically are unnecessary.

Summario in Interlingua

In tres patientes—un infante, un puero, e un adulto—con sever stenosis valvular, le pression systolic dextero-ventricular esseva plus que 100 mm de Hg post valvotomia effectuate sub hypothermia a transverso un apertura in le arteria pulmonar. Le mesuration de pressiones permitteva le localisation del remanente obstruction in le via de effluxo ab le ventriculo. Le exploration intracardiac de iste region indicava que le obstruction non esseva rigide. Illo pareva esser le effecto de un contraction del musculo hypertrophiate. In le curso de inter 6 e 12 menses post le operation, le signos cardiographic de hypertrophia dextero-ventricular dispareva, e catheterisationes cardiac effectuate inter 10 e 15 menses post le operation revelava pressiones intra le limites normal in le ventriculo dextere e solmente leve o nulle gradientes transvalvular.

Il pareva que le sever stenosis valvular esseva responsabile pro le marcate grados de hypertrophia in le pariete del ventriculo dextere e que iste hypertrophia sufficeva a restringer le via de effluxo post que le obstruction valvular habeva essite alleviate. Le restauration del function valvular per valvoplastia reduceva le labor del ventriculo de maniera que le hypertrophiate fibras myocardial retornava a dimensiones plus proxime

il norma con le effecto de un complete re-
gression de iste forma secundari de stenosis
infundibular.

Ab le puncto de vista chirurgic, le con-
clusion a derivar ab iste observationes es le
sequente: Quando le valvula ha essite aperite
completemente, nulle effortio additional a
corriger le stenosis muscular per medios
chirurgic es necessari, excepte in casos in
que il existe un obstruction fixe como per
exemplo un diaphragma o un anulo.

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Hence, since a man may make experiment in many places, it appears that the function of the portal in the veins is the same as that of the Sigmoides, or three pointed portals, which are made in the orifice of the aorta or vena arteriosa, to wit that they may be closely shut up, lest they should hinder the blood to return back again.—William Harvey. *De Motu Cordis*, 1628.

Electrocardiograms of Ninety Patients with Acrosclerosis and Progressive Diffuse Sclerosis (Scleroderma)

By JOHN H. WINDESHEIM, M.D., AND THOMAS W. PARKIN, M.D.

The records of all patients with scleroderma seen at the Mayo Clinic during the years 1949 through 1953 were reviewed. There were 90 who had electrocardiograms available for study. The diagnosis in 63 patients was acrosclerosis and 27 were diagnosed as having progressive diffuse sclerosis.

ALTHOUGH Heine[1] described the first case of sclerodermatous heart disease in 1926, this entity did not seem to be well established until 1943, when Weiss and associates[2] described and discussed the problem. Since then many articles have appeared in the literature pertaining to the clinical and pathologic aspects of the disease process known as "scleroderma." In addition, the electrocardiographic abnormalities that may occur have been described in detail. In our review of the literature it became apparent that most of the electrocardiograms were from patients with far-advanced scleroderma who died as a result of this disease process. In many instances the clinical picture indicated cardiac involvement because there were signs and symptoms of congestive heart failure. Necropsy studies have permitted a clinicopathologic correlation between the electrocardiographic patterns and the disease process within the heart. It therefore seemed to us that this particular aspect of the problem had been well documented.

However, we have been unable to find many articles pertaining to the incidence of normal and abnormal electrocardiograms in a large series of patients with *all stages* of scleroderma and in whom the electrocardiograms were studied, whether or not there was clinical evidence to suspect cardiac involvement by scleroderma. Therefore, the purpose of our study was to determine the incidence of normal and abnormal electrocardiograms in a large series of patients with all stages of scleroderma but particularly those with acrosclerosis. Before proceeding with a report of our study we should like to summarize our review of the literature with regard to the electrocardiogram in patients with scleroderma.

The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

REVIEW OF THE LITERATURE

Weiss and associates[2] discussed 9 cases with cardiac involvement. Electrocardiographic tracings were recorded in 8 of these patients and all were found to be abnormal. There were 3 tracings showing premature ventricular beats, 3 with low voltage, 2 with "partial bundle-branch block," 2 with left bundle-branch block, 2 with left ventricular hypertrophy, and 1 with atrial fibrillation. The electrocardiogram of Mathisen and Palmer's[3] patient with proved cardiac involvement showed extrasystoles, left axis deviation, atrioventricular conduction of 0.24 second, slurred low-voltage QRS, and diphasic T with depressed RST in lead I. East and Oram's[4] patient also had abnormal electrocardiographic findings with widened P-R interval, occasional atrial premature beats, and slurred widened QRS complex. Complete heart block and ventricular extrasystoles later developed.

Another case of sclerodermatous heart disease with necropsy findings was described by Spain and Thomas.[5] The only abnormal electrocardiographic findings were a P-R interval of 0.21 to 0.28 second and a QRS interval of 0.08 to 0.11. Gil,[6] in a study of 8 patients with sclerodermatous heart disease, found electrocardiographic changes in 7.

TABLE 1.—*Age and Sex Distribution of Ninety Patients with Acrosclerosis and Chronic Progressive Sclerosis (Scleroderma)*

Age, yr.	Male		Female		Total	
	Number	Per cent	Number	Per cent	Number	Per cent
0–9	0	0	1	1.6	1	1.1
10–19	1	3.4	1	1.6	2	2.2
20–29	0	0	8	13.1	8	8.9
30–39	4	13.8	16	26.3	20	22.3
40–49	6	20.7	15	24.6	21	23.3
50–59	8	27.6	13	21.3	21	23.3
60–69	9	31.1	7	11.5	16	17.8
70–79	0	0	0	0	0	0
80–89	1	3.4	0	0	1	1.1
Total	29	100.0	61	100.0	90	100.0
Youngest	17 yr.		9 yr.		9 yr.	
Oldest	87 yr.		69 yr.		87 yr.	
Mean	53 yr.		43 yr.		46 yr.	

TABLE 2.—*Electrocardiograms of Ninety Patients with Atherosclerosis and Progressive Diffuse Sclerosis (Scleroderma)*

Characteristics of electrocardiograms	Cases	
Normal		82
Abnormal		8
Anterior myocardial scar suggested	2	
Low-voltage QRS complexes with gross T-wave abnormalities	2	
Atrial fibrillation	1	
Minor intraventricular conduction defect with T-wave change	1	
Complete right bundle-branch block with prolonged P-R interval	1	
Left ventricular hypertrophy	1	
Total		90

There was incomplete right bundle-branch block in 3, complete right bundle-branch block in 1, and "myocardial changes" in 3. Hutcheson[7] stated that, of 8 cases of scleroderma studied, all had clinical or laboratory evidence of cardiac involvement. One patient showed right bundle-branch block, and another had low voltage and premature ventricular beats. Truelove and Whyte[8] thought that the heart was probably involved in 1 of their patients. The electrocardiogram showed negative T_2 and T_3; and R_3 varied from one complex to another, sometimes well marked, at other times, nonexistent. Hurly and associates[9] presented 1 case with marked congestive failure secondary to sclerodermatous involvement of the heart. The electrocardiogram showed low voltage in the limb leads, first-degree heart block, low R waves in leads V_1 to V_4, and low T waves in the precordial leads. In a later tracing there was disappearance of the R wave in V_1 to V_4 and depressed S-T segment in V_5 and V_6.

Three cases of scleroderma with involvement of the heart, proved at necropsy, were discussed by Goetz.[10] The electrocardiogram of one patient showed atrial fibrillation with multifocal extrasystoles and low voltage, the second had inverted T_2 and T_3, whereas the third patient had an electrocardiogram within normal limits.

Barritt and O'Brien[11] reported 2 cases with involvement of the heart by generalized scleroderma. One patient had cardiac failure and possible pericardial effusion, but the other had no cardiorespiratory symptoms or signs. The electrocardiogram of the former demonstrated depressed S-T segments over the left ventricle with flat T waves. That of the latter patient showed inverted T waves in V_1 to V_4.

TABLE 3.—*Clinical Data of Eight Patients with Acrosclerosis or Progressive Diffuse Sclerosis (Scleroderma) and Abnormal Electrocardiograms*

Patient	Age, yr., and sex	Duration of symptoms	Electrocardiographic pattern	Cardiorespiratory symptoms	Chest roentgenogram	Esophageal involvement
1*	56 M	7 years	Atrial fibrillation	Effort dyspnea	Mitral stenosis	Yes
2*	60 M	3 years	Left ventricular hypertrophy	Angina pectoris	Normal	No
3*	42 F	4 years	Minor intraventricular conduction defect with T-wave change	None	Minimal cardiac enlargement	Yes
4*	59 M	8 months	Anterior wall scar suggested	Effort dyspnea	Fibrosis of both lung bases	No
5*	51 F	2 years	Anterior wall scar suggested	None	Normal	Yes
6†	42 F	2 years	Low-amplitude QRS complexes with gross T-wave abnormalities	Dyspnea	Cardiac enlargement. Diffuse pulmonary fibrosis	Yes
7†	28 F	3 years	Low-amplitude QRS complexes with gross T-wave abnormalities	Dyspnea	Cardiac enlargement. Rib atrophy	Yes
8†	64 M	6 years	Right bundle-branch block	Effort dyspnea	Cardiac enlargement	Yes

* Acrosclerosis.
† Progressive diffuse sclerosis.
All patients had Raynaud's phenomena except patient 4.

Another case was presented at a clinicopathologic conference in the Barnes Hospital.[12] The electrocardiogram showed only left ventricular strain and sinus tachycardia, although marked myocardial fibrosis was found at necropsy.

Beigelman and associates[13] noted no diagnostic electrocardiographic changes in 14 patients with progressive systemic sclerosis, although all had some cardiorespiratory symptoms. They stated that most findings were nonspecific, including T-wave inversion, prolonged Q-T interval, low voltage, and various arrhythmias, principally premature beats.

Serial electrocardiograms in another patient with generalized scleroderma showed low voltage, supraventricular premature beats, and transient episodes of right bundle-branch block.[14]

Mustakallio and Sarajas[15] collected electrocardiograms in 7 cases of scleroderma without regard to their cardiac status and found only nonspecific changes. They concluded that, since none of their cases showed low amplitude of multiple leads, the sclerodermatous process, if present in the heart at all, would not be very extensive.

Boyd and associates[16] reviewed 63 cases of scleroderma. The electrocardiographic studies in an unspecified number of these patients showed both right and left axis deviation and frequent conduction defects, and in several instances bundle-branch block was present.

In a recent review by Leinwand and associates[17] of a large group of patients with scleroderma, abnormal electrocardiograms were obtained in 5 of 51 patients so examined and 20 showed minor changes of possible significance. It was noted that postmortem examination of the heart showed more extensive changes than anticipated, even in patients with normal electrocardiograms. There were few patients who did not reveal some charac-

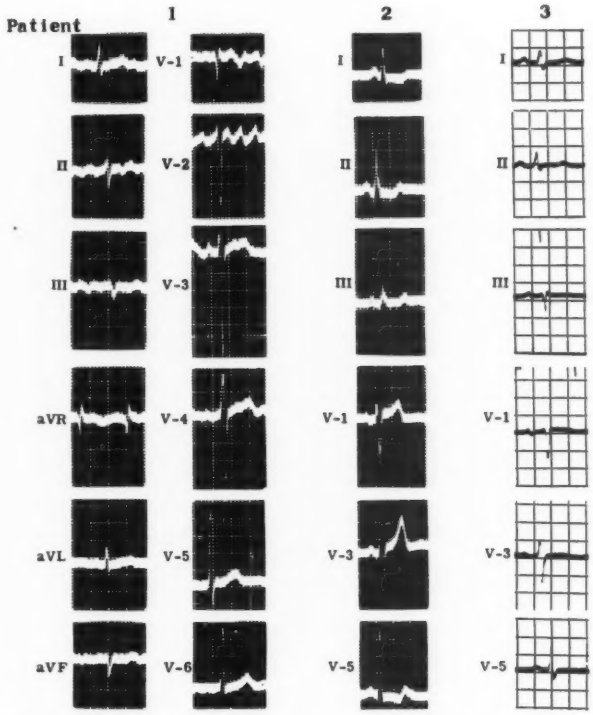

FIG. 1. Electrocardiograms of 3 patients with acrosclerosis. That of patient 1, who also had mitral stenosis, reveals atrial fibrillation. The tracing of patient 2 is indicative of left ventricular hypertrophy and that of patient 3 reveals a minor intraventricular conduction defect with low-amplitude T waves.

teristic pathologic change at necropsy, whether or not clinical or electrocardiographic signs were present.

METHODS

We reviewed the records of all patients with scleroderma seen at the Mayo Clinic during the years 1949 through 1953. All cases were included whether or not the patients had symptoms or signs referable to the cardiovascular system.

The records of 205 consecutive patients were reviewed. Each patient had been seen by a member of the Section of Dermatology or of the section dealing with peripheral vascular diseases or of both. The records of 105 patients indicated that no electrocardiogram had been taken. There remained a group of 100 patients who had electrocardiograms available for study. The diagnosis in 63 patients was acrosclerosis. Of the remaining 37 patients, 27 were diagnosed as having progressive diffuse sclerosis and 10 were not used in our survey because of some unusual features about the problems that left the final accurate diagnosis in doubt.

A number of features of each patient's problem were noted and given consideration in order to evaluate changes in the electrocardiogram more accurately. The age and sex distribution is listed in table 1. Special note was made of abnormalities on chest roentgenograms, the arterial blood pressure, history of Raynaud's phenomena and the duration of such, if present, symptoms and signs referable to the cardiovascular system, ingestion of such drugs as digitalis and quinidine at the time when the electrocardiograms were taken, and the presence of cerebral, pulmonary and esophageal involvement.

All of the patients had electrocardiograms consisting of standard leads I, II, and III and precordial leads V_1, V_3, and V_5. A few also had the unipolar extremity and precordial leads V_1 through V_6.

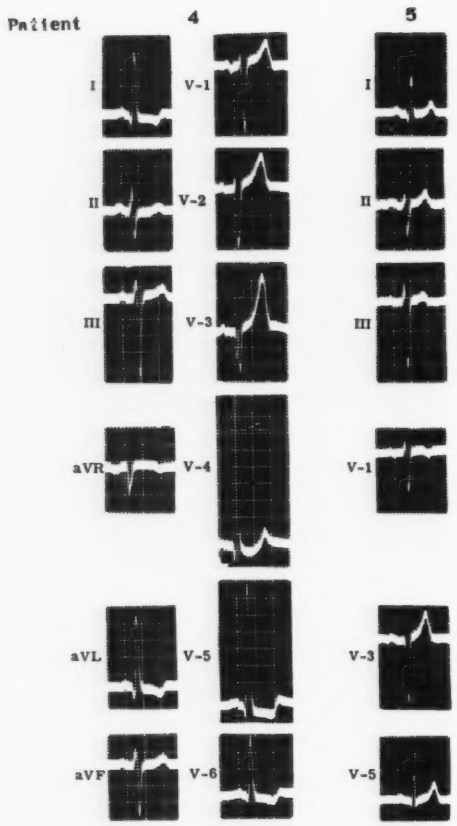

FIG. 2. Electrocardiograms of 2 patients with acrosclerosis. Both of these are suggestive of a scar in the anterior wall of the left ventricle. That of patient 4 would also be indicative of left ventricular hypertrophy.

RESULTS

Eighty-two patients had normal electrocardiograms, and 8 tracings were considered abnormal. Only 5 of the 63 patients with acrosclerosis and 3 of the 27 patients with progressive diffuse sclerosis had abnormal electrocardiograms. The abnormalities are listed in table 2. It is to be noted that such patterns can be found in a wide variety of cardiac diseases and that in themselves they are not really pathognomonic of a specific heart lesion and must be interpreted with respect to all the aspects of the patient's problem.

Clinical data pertaining to the 8 patients with abnormal electrocardiograms are shown in table 3. Five of these patients (cases 1, 2, 3, 4, and 5) were thought to have acrosclerosis. Their electrocardiograms are shown in figures 1 and 2. There was nothing at the time of the clinical examination to suggest sclerodermatous heart disease, but 1 of the patients had mitral stenosis, which could of course account for the atrial fibrillation. Three patients (cases 6, 7, and 8) had progressive diffuse sclerosis. Their electrocardiograms are shown in figure 3. There was clinical evidence to suggest cardiac failure in 2 of them (cases 6 and 7). These 2 patients had electrocardiograms showing low-amplitude QRS complexes with gross T-wave abnormalities in multiple leads, which usually indicate the presence of an extensive cardiac disease process.

DISCUSSION

When one reviews the literature on scleroderma, it is immediately apparent that many aspects of the problem remain unknown. This applies particularly to the etiology of the disease. Another problem that appears pertains to the terminology used in the literature. Such terms as "sclerodactyly," "scleroderma," "acrosclerosis," "acroscleroderma," "generalized scleroderma," "diffuse scleroderma," and "progressive systemic sclerosis" are used. There are different opinions as to whether one is justified in separating the patients into different categories. The different classifications may be simply a matter of definition and the patients may have the same disease but simply different degrees thereof. Nevertheless, we separated our patients into 2 groups, acrosclerosis and progressive diffuse sclerosis.. The term "acrosclerosis" refers to those patients with or without Raynaud's phenomena who have scleroderma limited to the face, chest, and extremities. When the disease process extends over wide regions of the body, the term "progressive diffuse sclerosis" is used.

All but 3 of the 58 patients with acrosclerosis and normal electrocardiograms had Raynaud's phenomena. Of the 5 patients

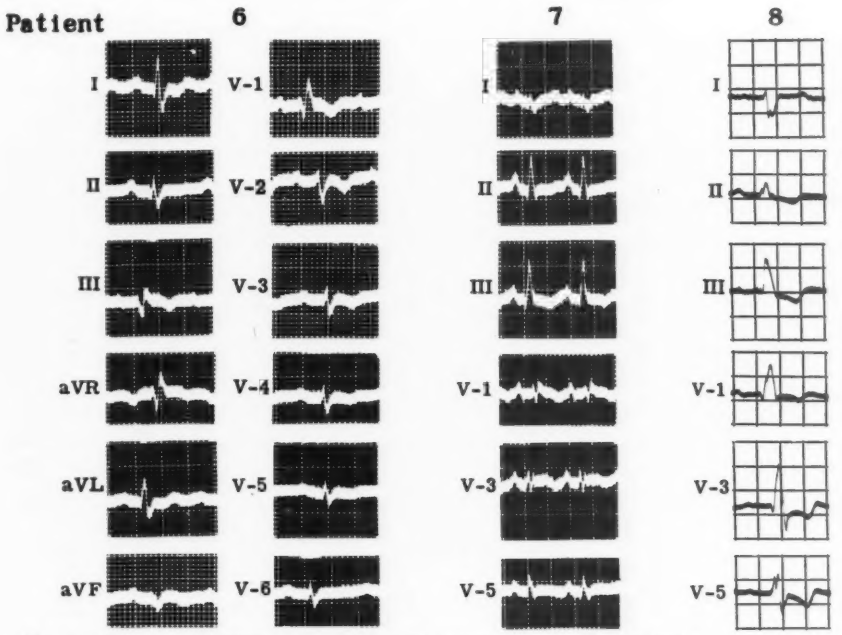

FIG. 3. Electrocardiograms of 3 patients with progressive diffuse sclerosis. The tracings of patients 6 and 7 show low-amplitude QRS complexes with gross T-wave abnormalities. The electrocardiogram of patient 8 reveals an intraventricular conduction disturbance of the right bundle-branch block type and T-wave inversion in the precordial leads.

with acrosclerosis and abnormal electrocardiograms, 4 had Raynaud's phenomena. There were 3 instances of incomplete right bundle-branch block of the type belonging to group I (as defined by Barker and Valencia[18]) in the patients with acrosclerosis. Such incomplete right bundle-branch block patterns do not necessarily represent organic heart disease, for the pattern might be due to physiologic late activation of the base of the right ventricle or crista supraventricularis.

There was no significant correlation between the known duration of scleroderma and the types of electrocardiographic patterns. It might be noted that the known duration of the scleroderma in the 2 patients with electrocardiographic patterns indicating old infarctions of the anterior wall of the left ventricle was 8 months and 2 years. We use the term "infarction," realizing however that such patterns simply indicate a loss of viable myocardium (transmural) beneath the exploring electrodes. It is known that several disease processes affecting the myocardium other than infarctions due to insufficiency of the coronary circulation can produce similar patterns; for example, amyloidosis, hemochromatosis, and scleroderma. Without gross and microscopic examinations of the heart we cannot be certain about the exact lesions present.

There were 27 patients classified as having progressive diffuse sclerosis. Fourteen of the 24 patients with normal electrocardiograms had Raynaud's phenomena.

The sclerotic process is known to affect many organ systems of the body such as the skin, lungs, heart, gastrointestinal tract, and kidneys. The clinical course and manifestations are varied. It is well established now that the heart may be affected and some patients can die as a result of this involvement.

The pathologic changes characterizing sclerodermatous heart disease have been described many times.[10, 13, 14, 19, 20] It is not our intension to discuss such pathologic changes, but

a few remarks in this regard seem appropriate. The pericardium and myocardium may show varying degrees of fibrosis. The increase in connective tissue in the myocardium may vary from slight interstitial cellular fibrosis to large dense (hyaline) scars. It is of interest to note that the pericardium may be affected as well as the myocardium.[19, 21]

Such lesions in the heart should theoretically produce a variety of changes in the electrocardiogram[22] depending upon the location and extent of the pathologic process. However, one would expect a number of different types of other disease processes that affect the heart to be capable of producing the same types of electrocardiographic abnormalities.

From the review of the literature it is apparent that the electrocardiograms of patients with scleroderma may be normal or may present a variety of abnormalities, such as arrhythmias, a decrease in amplitude of the QRS complexes in multiple leads, depression of S-T segments, decrease in amplitude or inversion of T waves, and disturbances in atrioventricular and intraventricular conduction. It is also to be noted that postmortem examinations have revealed sclerodermatous changes in the heart in patients with normal electrocardiograms.[17]

Summary

The electrocardiograms of 90 patients with scleroderma were reviewed. There were 63 patients with acrosclerosis, of whom 5 had abnormal electrocardiograms (8 per cent). These abnormalities consisted of patterns suggesting an anterior wall scar (2), atrial fibrillation (1), left ventricular hypertrophy (1), and a minor intraventricular conduction defect with T-wave change (1). There were 27 patients with progressive diffuse sclerosis, of whom 3 had electrocardiographic abnormalities (11 per cent), consisting of low-amplitude QRS complexes with gross T-wave changes (2), and complete right bundle-branch block (1). The 2 patients with the low-amplitude QRS complexes and T-wave changes in multiple leads had clinical evidence of congestive heart failure.

Summario in Interlingua

Esseva scrutiniate le electrocardiogrammas de 90 patientes con scleroderma. Le serie includeva 63 patientes con acrosclerosis, e 5 de istes (8 pro cento) habeva electrocardiogrammas anormal. Le anormalitates consisteva de configurationes que suggereva cicatrice del pariete anterior (2 casos), fibrillation atrial (1 caso), hypertrophia sinistro-ventricular (1 caso), e un minor defecto de conduction intraventricular con alteration del unda T (1 caso). Le serie includeva 27 patientes con progressive sclerosis diffuse. Tres de istes (11 pro cento) habeva anormalitates electrocardiographic, consistente de complexos QRS a basse amplitude con grossier alterationes del unda T (2 casos) e bloco complete de branca dextere (1 caso). Le 2 patientes con complexos QRS a basse amplitude e alterationes de unda T in derivationes multiple exhibiva evidentia clinic de congestive insufficientia cardiac.

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In 1773, John Hunter had his first attack, which was graphically described by his nephew, Everard Home: "While he was walking about the room he cast his eyes on the looking-glass, and observed his countenance to be pale, his lips white, giving the appearance of a dead man. This alarmed him and led him to feel for his pulse, but he found none in either arm; the pain continued, and he found himself at times not breathing. Being afraid of death soon taking place if he did not breathe, he produced the voluntary act of breathing by working his lungs by the power of the will." In 1776 he had a second attack, and when convalescent he visited Bath. Here he was seen by his friend and pupil, Edward Jenner, of Berkeley; and one of the most interesting and sagacious letters of that distinguished man was written to Heberden, giving his diagnosis of John Hunter's case, and suggesting, for the first time, the probable association of disease of the coronary arteries with angina pectoris.—William Osler. *Lectures on Angina Pectoris and Allied States*, 1897.

A Method for the Electrocardiographic Recognition of Atrial Enlargement

By RADI MACRUZ, M.D., JOSEPH K. PERLOFF, M.D., AND ROBERT B. CASE, M.D.

New criteria for the electrocardiographic recognition of right atrial enlargement, left atrial enlargement, and combined atrial enlargement were studied in 110 patients with congenital and acquired heart disease. Precise physiologic data were available in all cases. The method of analysis was designed for application to conventional scalar electrocardiography and hence can be used without modification for routine clinical purposes.

THE current criteria for the electrocardiographic diagnosis of atrial enlargement are seldom adequate for the recognition of even moderate increases in chamber size that may be detectable radiologically. Analysis of tracings has principally considered the configuration, amplitude, and duration of P waves. Although prolongation of P-R interval has also been observed in severe pulmonic stenosis,[1] atrial septal defect,[2] Ebstein's disease,[3] and atrioventricularis communis,[4] attention thus far has not specifically been directed toward the P-R segment (time between end of electric atrial systole and onset of electric ventricular systole). This communication proposes a new basis for the diagnosis of atrial enlargement based upon the relation between the durations of P wave, P-R segment, and P-R interval.

MATERIALS AND METHODS

The electrocardiograms of 62 normal adults and 110 patients with congenital or acquired heart disease were analyzed.

This case material is summarized in table 1. The patients were divided into 2 groups—those with diseases in which an increase in left atrial size might be expected and those with diseases in which an increase in right atrial size might be expected. These will subsequently be designated "left atrial group" and "right atrial group."

The width of the P wave and the durations of P-R interval and P-R segment were each measured in lead II according to the following criteria. When the P-R segment was flat, it was measured from the end of the P wave to the onset of the QRS complex. Occasionally the P-R segment was found to slope downwards to the QRS complex, and in this case the onset of the P-R segment was considered to be the point where a line extended from the T-P segment intersected the descending limb of the P wave. The P-R interval was measured from the onset of the P wave to the onset of the QRS complex. Width of the P wave was measured from the onset of the P wave to the onset of the P-R segment. In conventional single channel scalar electrocardiography, the most accurate P-R interval is the sum of the maximum P wave duration (in any lead) plus the minimum P-R segment duration (in any lead). This largely obviates the need for simultaneous leads. When this method was applied to our tracings, it was determined that lead II reflected the correct P-R interval with sufficient frequency to warrant its selection for the type of analyses described in this study.[5]

The evaluation of all patients included fluoroscopy, x-ray, electrocardiogram, and right heart catheterization. In 7 patients with mitral valve disease right heart catheterization was omitted. The left heart was catheterized by the bronchoscopic technic in these 7 patients and in other cases when indicated.* Angiocardiography and retrograde aortography were performed in selected cases.

None of the normal and only 5 of the congenital group were receiving digitalis when the tracings were taken. Two of the 6 patients with primary pulmonary hypertension and 65 per cent of those with mitral valve disease were on maintenance doses of digitalis at the time that their tracings were recorded. No tracings were taken during administration of quinidine. Heart rates varied from 60 to 150 beats per minute, a range that was considered to exert negligible rate effect on the P-R intervals.[6] The same patients were occasionally analyzed at materially different rates

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*The left heart catheterizations were done by Dr. Andrew Glenn Morrow, Chief, Surgery, National Heart Institute, National Institutes of Health.

with no significant variation in P-R interval or P/PR segment ratio.

Results

In the series of normal adults, the P-R interval varied from 0.12 to 0.20 second. It should be noted that there was only 1 case below 0.14 second. The P wave varied from 0.06 to 0.11, with only 1 case above 0.10. The mean values were 0.09 second for the P wave, 0.16 second for the P-R interval, and 0.07 second for the P-R segment. The ratio of the duration of the P wave to the duration of the P-R segment varied from 1.0 to 1.6, with a mean value of 1.2.

The duration of the P-R interval in patients over 16 years of age was compared in the normal, right atrial, left atrial, and uncomplicated left atrial groups (table 2). This last group consisted of left atrial cases in which pulmonary arteriolar resistance was normal and hence in which right atrial enlargement might *not* be expected. The 22 uncomplicated left atrial cases contained 17 with mitral valve disease, 2 with aortic stenosis, and 1 with ventricular spetal defect.

The mean ages of all groups were approximately the same. The mean P-R interval in the right atrial group was 0.20 second, a statistically significant increase from the normal of 0.16 second. Duration of the P-R interval in the left atrial group was identical to that in the normal. However, in the uncomplicated left atrial group it was 0.15 second, a statistically significant decrease from the normal.

The average duration of the P wave in adults was found to be 0.09 second in the right atrial group and 0.11 second in the left atrial group. The ratio of P wave to P-R segment was determined in all cases.

As stated before, the mean value of the P/PR segment ratio in our group of normal adults was found to be 1.2, with a range of 1.0 to 1.6. From Ziegler's data for children[7] the P/PR segment ratio was calculated by us, and found to be a mean of 1.2 from birth to 16 years. It is interesting to note the constancy of the P/PR segment ratio in spite of the wide changes in P-wave duration and P-R interval that occur with age.

TABLE 1.—*Summary of Clinical Data*

Diagnosis	Number of cases	Mean age (years)	Age range (years)
Right atrial cases			
Atrial septal defect	16	20 ± 10	3–49
Atrial septal defect with anomalous venous drainage	3	27 ± 11	6–34
Atrial septal defect with pulmonic stenosis	4	7 ± 3	1–11
Pulmonic stenosis	9	11 ± 5	6–30
Primary pulmonary hypertension	6	31 ± 9	14–
Ebstein's disease	1	—	18
Ruptured aneurysm of sinus of valsalva into right atrium	1	—	26
Tetralogy of Fallot	7	6 ± 3	2–15
Total	47		
Left atrial cases			
Ventricular septal defect	10	12 ± 6	2–23
Patent ductus arteriosus	9	19 ± 14	1–40
Coarctation of aorta	3	20	2–29
Acquired aortic stenosis	2	26	21–31
Congenital aortic stenosis	3	9 ± 2	7–31
Eisenmenger's complex*	1	—	31
Congenital mitral incompetence	1	—	5
Rheumatic mitral incompetence	13	39 ± 8	21–59
Rheumatic mitral stenosis	18	37 ± 6	17–49
Aortic incompetence with mitral valve disease	3	44 ± 7	36–55
Total	63		
Normal	62	33 ± 8	18–59

*This case can be considered in either left atrial or right atrial groups.

Figure 1 illustrates the separation of left atrial and right atrial cases in relation to the normal P/PR segment ratio of 1.0 to 1.6. There is striking separation of the right atrial cases below the normal mean and of the left atrial cases above the normal mean. However, 22 of the cases in the right atrial group and 17 of the cases in the left atrial group fell within the normal range, 1 of the latter having a ratio of less than 1.0. The right atrial section in figure 1 is separated into the individual disease states, from 1 through 6 as

TABLE 2.—*Comparisons of P-R Intervals in All Four Groups*

Diagnosis	Number of cases	Age (mean)	P-R interval (mean)	Value of p in relation to normal	Result
Normal	62	33 ± 8	0.161 ± 0.01	—	—
Total right atrial cases	19	29 ± 7	0.195 ± 0.03	$p < .001$	Significantly longer than normal
Total left atrial cases	47	36 ± 9	0.162 ± 0.03	—	—
Uncomplicated left atrial cases	22	33 ± 10	0.149 ± 0.02	$p < .001$	Significantly shorter than normal

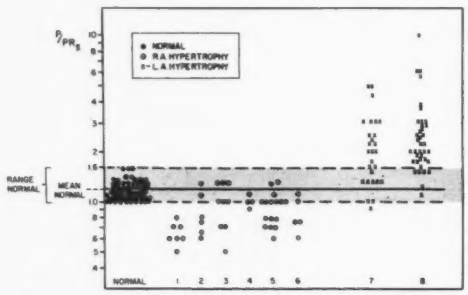

FIG. 1. Distribution of the right atrial and left atrial groups about the normal. Ratio of duration of P wave to duration of P-R segment is plotted in the ordinate. Numbers on the abscissa refer to the following groups: 1. Tetralogy of Fallot. 2. Primary pulmonary hypertension. 3. Pulmonic stenosis. 4. Pulmonic stenosis with atrial septal defect. 5. Atrial septal defect. 6. Atrial septal defect with anomalous venous drainage, Ebstein's disease, ruptured aneurysm of the sinus of Valsalva into the right atrium. 7. and 8. Left atrial group: 7, congenital; 8, acquired.

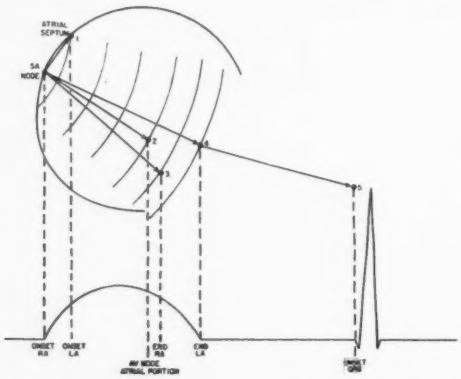

FIG. 2. Diagram of transmission of impulse from S-A node.

described in the legend. The left atrial section is divided into the congenital cases (group 7) and acquired cases (group 8).

DISCUSSION

Explanation of the changes in P duration, P-R interval, P-R segment, and P/PR segment ratio that occur with atrial enlargement might be approached in the following way. Atrial activation is considered to follow the pattern schematically illustrated in figure 2. The depolarization originates in the sinoatrial node (SA) and proceeds through the atrial muscle in concentric waves. After an interval it arrives at the atrial septum and initiates left atrial depolarization (point 1), followed in temporal sequence by arrival at the AV node (point 2), by completion of right atrial depolarization (point 3), and finally by completion of left atrial depolarization (point 4). The linear velocity of this impulse is about 1,000 mm. per second.[8-9] If this velocity remained relatively constant,* right atrial enlargement would then increase the transit time from SA node to AV node and prolong both P-R interval and P-R segment (fig. 3) (fig. 4, nos. 5-10). However, the duration of the P wave would be unaffected, since the terminal part of the P wave is normally written by left atrial depolarization. Thus, right atrial enlargement would prolong the P-R interval and alter the configuration of the P wave but would not affect P-wave duration except for those instances in which transit time in the right atrium was exceptionally prolonged by the magnitude of chamber size. The terminal portion of the P wave would then be written by the *right* atrium, resulting in P-wave prolongation. That this possibility may occur is supported by the observation of a

*If velocity were impeded by an intra-atrial conduction defect, then P-R interval or P duration or both might be prolonged, depending upon the respective involvement of right or left atrial conduction.

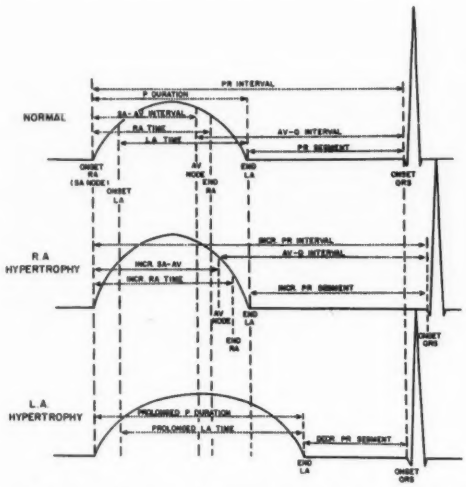

FIG. 3. Diagram of transmission of impulse from S-A node in normal, right atrial enlargement, and left atrial enlargement.

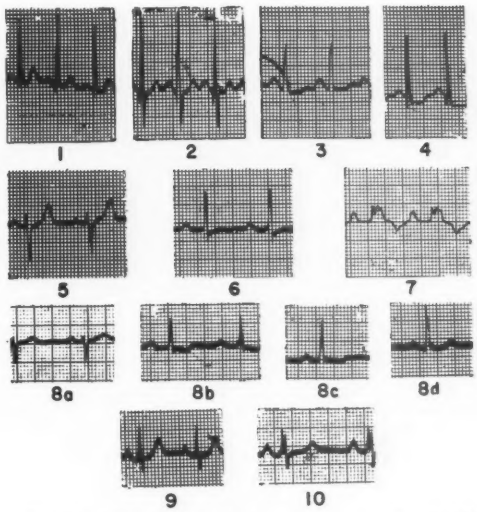

FIG. 4. Illustrative electrocardiograms (lead II) from the following cases: (1) patent ductus arteriosus, (2) coarctation of the aorta; (3) mitral stenosis; (4) congenital mitral incompetence; (5) atrial septal defect with pulmonic stenosis (the P/PR segment ratio is normal but the P-R interval is prolonged for age group); (6) primary pulmonary hypertension; (7) Ebstein's disease; (8) rupture of an aneurysm of the sinus of Valsalva into the right atrium—(*a*) before rupture, (*b*) after rupture but before operative repair, (*c*) 2 weeks postoperative; (*d*) 10 weeks postoperative; (9) tetralogy of Fallot; (10) atrial septal defect (P-R interval prolonged for age group).

decrease in P-wave duration following valvotomy for pulmonic stenosis.[10]

Left atrial enlargement, on the other hand, should exert no influence on the transmission time from the SA to the AV node, and hence should be associated with a normal P-R interval (fig. 3). However, the P-wave duration might be prolonged by the increased transit time through the enlarged left atrium because, as noted above, the left atrium normally writes the terminal inscription of the P wave. The net result should be prolongation of the P wave and shortening of the P-R segment but no change in P-R interval. Indeed, the P-R segment may virtually disappear (fig. 4, nos. 1-4). Gross evidence of the validity of these observations is seen in the P-wave pattern of "P pulmonale"—with its high amplitude, normal duration, and prolonged P-R interval and P-R segment; and in the P-wave pattern of "P mitrale"—with its delayed secondary peak (bifid), prolonged duration, normal P-R interval, and shortened P-R segment.

If both atria are hypertrophied, it might be expected that the co-existence of the prolonged P-R segment of right atrial enlargement and the prolonged P duration of left atrial enlargement would counterbalance each other resulting in a normal P/PR segment ratio. Hence when the P/PR segment ratio is normal, the finding of distinct prolongation of P-R interval and P duration identifies the presence of combined atrial enlargement. This is consistent with the observation that as both right and left atrial masses increase from infancy to adult life there is an increase in P-R interval, P duration, and P-R segment. As noted, if depolarization in an enlarged right atrium is unusually prolonged because of a markedly increased chamber size, the terminal portion of the P wave may be written by the *right* rather than the *left* atrium. In this study right atrial enlargement was found to prolong the P duration to a maximum of 0.12 second in adults and 0.10 second in children (Ziegler's tables[6] were referred to for normal P duration below the age of 16 years). Fur-

ther prolongation of P duration was seen only when the left atrium was enlarged. It should be emphasized, therefore, that the 22 cases in the right atrial group and the 17 cases in the left atrial group that had normal P/PR segment ratios must be analyzed further according to the foregoing criteria for combined enlargement or right atrial enlargement with prolonged P duration.

Figure 1 illustrates the specific distributions of P/PR segment ratio in all categories. The cases with ratios of less than 1.0 are in the group with right atrial enlargement and those with ratios above 1.6 are in the group with left atrial enlargement. The cases in the range of 1.0 to 1.6 include normal adult controls, cases of combined atrial enlargement, and cases of right atrial enlargement with prolonged P duration.

Among the normal adult controls (fig. 1) it was found that although P duration and P-R interval varied with age, the P/PR segment ratio remained constant irrespective of age.

None of the cases of tetralogy of Fallot (category 1) fell into the normal range. Indeed, this category had the smallest P/PR segment ratio in the entire study. This appeared to be a consequence of unusually short P durations that averaged 0.06 second compared to a mean P duration of 0.08 second for all other right atrial cases in the same age group.

In category 2 (primary pulmonary hypertension), 2 cases had normal ratios. One of these had a pulmonary artery pressure of 70/30, the lowest in this category. Right atrial enlargement was not evident by any electrocardiographic criteria. The other patient was a 14-year-old child with a pulmonary artery pressure of 180/118, P-wave amplitude upper limits of normal, a P-R interval of 0.18, and a P duration of 0.10. For this age group the mean normal P-R interval is 0.15 and the mean normal P duration is 0.08.[6] This patient, therefore, would be suspected by the above criteria to have right atrial enlargement not otherwise evident.

In category 3 (pulmonic stenosis), 6 cases were in the normal range. One represented right atrial enlargement with prolonged P duration. Four were normal by all electrocardiographic criteria; 2 of these were mild, 1 was severe. The sixth case, one of severe stenosis, was normal by our criteria but had a P amplitude increased to 3.6 mm.

In category 4 (pulmonic stenosis with atrial septal defect) all 3 cases in the normal range represented right atrial enlargement with prolonged P duration.

In category 5 (atrial septal defect), 9 cases had normal P/PR segment ratios. Two represented right atrial enlargement with prolonged P duration, 3 had P durations that were the upper limits of normal, and 4 were normal by all criteria.

In category 6 (atrial septal defect with anomalous venous drainage, Ebstein's disease, congenital aneurysm of the sinus of Valsalva with rupture into the right atrium), the 2 cases in the normal range were atrial septal defects with anomalous venous drainage, one representing right atrial enlargement with prolonged P duration, the other (with a small shunt) normal by all criteria.

In category 7 (congenital cases with left atrial preponderance), 10 were within the normal range. One with Eisenmenger's syndrome (pulmonary artery pressure of 160/32) and another with a reversed shunt patent ductus arteriosus (pulmonary artery pressure 132/64) had no evidence of atrial enlargement by any electrocardiographic criteria. These remain unexplained. The single patient with coarctation of the aorta that fell into the normal range had a very slight brachial-femoral gradient, normal data on right heart catheterization, and therefore no evident physiologic basis for left atrial enlargement. The remaining 7 with normal ratios had ventricular septal defects. One of these had no electrocardiographic evidence of atrial enlargement in spite of a bidirectional shunt (predominant left-to-right), 2 were very mild, a fourth had a P duration the upper limits of normal, and the remaining 3 fulfilled the criteria for combined enlargement. The single case that fell into the P/PR seg-

ment range of right atrial enlargement had a patent ductus arteriosus with a pulmonary arterial pressure of 106/64 and reversal of the shunt.

In category 8, (acquired heart disease with the left atrial preponderance), 7 patients had normal P/PR segment ratios. One with severe aortic stenosis (gradient of 155 mm. Hg) and a left atrial pressure of 22/11 mm. Hg had no evidence of atrial enlargement by any electrocardiographic criteria. Of the 2 with severe mitral stenosis, one had a pulmonary artery pressure of 60/32, a P-R interval of 0.18 second, a P duration of 0.11 second, and no electrocardiographic criteria of atrial enlargement. The other had a P-R interval of 0.22 second and a P duration of 0.12 second, evidence of combined enlargement. The remaining 4 with normal P/PR segment ratios had mitral incompetence, 3 of which were mild. The fourth had a pulmonary artery pressure of 69/16, electrocardiographic evidence of right ventricular hypertrophy, a P-R interval of 0.20 second, and a P duration of 0.12 second. The increased P duration and upper normal P-R interval suggest combined enlargement.

In this same category, the adult cases with mitral valve disease or left-to-right shunts other than atrial septal defects, but with normal or slightly elevated pulmonary arteriolar resistances had P-R intervals significantly shorter than the comparable normal adult cases (table 2).

It appeared from the analysis of the cases with right atrial preponderance that the P-R interval prolongation occasionally was greater than could be accounted for by increased transit time through the enlarged right atrium. The following evidence suggests that right atrial hypertension may sometimes prolong the P-R interval and P-R segment by a selective effect on A-V conduction and hence explain this additional prolongation of P-R interval in these cases. A patient with a congenital sinus of Valsalva aneurysm that had ruptured into the right atrium had both enlargement and hypertension of the right atrial chamber. Before rupture the P-R interval was 0.16 second, the P-R segment 0.07 second (fig. 4, no. 8*a*). Immediately prior to operation (5 months after the first electrocardiogram), the P-R interval was 0.24 second, the P-R segment 0.15 second (fig. 4, no. 8*b*). Within 20 days after surgical closure of the rupture with a polyvinyl prosthesis,[11] the P-R interval fell to 0.20 second and the P-R segment to 0.11 second (fig. 4, no. 8*c*). Since the size of the right atrial wall could hardly have been altered significantly in so brief a period, it might be inferred that the shortening of the P-R interval correlated instead with a fall in atrial pressure. This shortening could be due either to more rapid conduction through the atrial muscle or to more rapid transit through the AV nodal tissue.

The effect that left atrial hypertension has on P-R interval and P-wave duration was further considered in the following way. In mitral stenosis the left atrial pressure is typically elevated. It was noted that the P-wave duration was unaffected by mitral valvulotomy.[12] This suggests that in the left atrium at least, the duration of electric systole is uninfluenced by the relief of atrial hypertension itself. Nor is there any immediate change after valvulotomy in P-R interval or P-R segment.[12] Hence, relief of left atrial hypertension appears to leave unchanged the velocity of conduction through its wall or through AV nodal tissue, whereas right atrial hypertension apparently may delay conduction through AV nodal tissue and hence prolong the AV to QRS interval.

Conclusions

The accepted range of normal for P-R interval is so broad that many patients with atrial enlargement fall within the normal range. Nor can one materially increase the accuracy of electrocardiographic diagnosis of atrial enlargement by analysis of the P-wave duration alone. However, when one observes the relative amount of the P-R interval occupied by the P wave—which can be expressed as the ratio $\frac{\text{P duration}}{\text{P-R segment}}$—the identification

of atrial enlargement becomes more precise. Normally the P duration is 50 to 60 per cent of the P-R interval for all heart rates up to age 16 years according to Ziegler[6] and above 16 years according to our data. That is, the ratio of $\frac{\text{P}}{\text{P-R segment}}$ varies within the narrow limits of 1.0 to 1.6.

In right atrial enlargement the P-R segment increases because of an increased transit time from the SA to the AV node. The P-wave duration remains constant, hence the ratio of P/PR segment falls below the normal range. When the right atrium is sufficiently enlarged so that the transit time of the depolarization impulse through that chamber is longer than the transit time of the depolarization impulse through left atrium, then the right atrium may write the terminal portion of the P wave. In this fashion, right atrial enlargement may also prolong the P duration as well as the P-R interval and hence increase both numerator *and* denominator of the fraction P/PR segment so that the resulting ratio may be normal. Right atrial enlargement was found to prolong the P duration to a maximum of 0.10 second in children and 0.12 second in adults. Hence, if the P/PR segment ratio is normal and the P-R interval prolonged, the associated finding of a P duration which though prolonged, does not exceed 0.10 second in the age group below 16 years and 0.12 second in the age group above 16 years, suggests the presence of right atrial enlargement.

In left atrial enlargement the terminal portion of the P wave is delayed because of the prolonged transit time of the depolarization impulse through the enlarged left atrial wall. Hence the P-wave duration is prolonged, the P-R segment is shortened, and P-R interval remains unchanged. The result is a P/PR segment ratio above the normal limit of 1.6.

In combined atrial enlargement the right atrium continues to prolong the P-R interval and the left atrium continues to prolong the P wave. Since these respective prolongations would increase both numerator and denominator of the fraction P/PR, it can be seen that in combined atrial enlargement the P/PR segment ratio may be normal. This occurs only in association with distinct absolute prolongation of P-R interval and P wave. Hence, when the $\frac{\text{P}}{\text{P-R segment}}$ ratio is normal in the presence of distinct prolongation of P-R interval and P-wave, combined atrial enlargement can be suspected. Though the P duration may overlap with the cases of right atrial enlargement with P-wave prolongation, if the P duration exceeds 0.10 second below the age of 16 years and 0.12 second above the age of 16 years, then this prolongation can be attributed to left atrial enlargement so that under these circumstances the associated finding of a normal P/PR segment ratio would establish the presence of combined atrial enlargement.

Summary

From an electrocardiographic study of 110 patients with congenital and acquired heart disease and 62 normal adults new criteria are suggested for the diagnosis of right atrial enlargement, left atrial enlargement, and combined atrial enlargement. Right atrial enlargement is present when the P/PR segment ratio is less than 1.0. Left atrial enlargement is present when this ratio is greater than 1.6. These values apply regardless of age group. The electrocardiographic criteria for combined atrial enlargement as well as a theoretical basis for these observations are also discussed.

Acknowledgment

The authors would like to express their appreciation to Dr. Robert P. Grant for his invaluable criticisms of this paper. May we further thank Dr. Andrew G. Morrow for making the physiologic data from his service so readily available, and Dr. John Smith of the Civil Aeronautics Association for the use of his files of normal electrocardiograms.

Summario in Interlingua

Super le base de un studio electrocardiographic de 110 patientes con congenite e acquirite morbo cardiac e de 62 adultos normal, nove criterios es suggerite pro le diagnose de

allargamento dextero-atrial, allargamento sinistro-atrial, e allargamento atrial combinate. Allargamento dextero-atrial es presente quando le proportion del segmentos P a Pr es minus que 1,0. Allargamento sinistro-atrial es presente quando iste proportion es plus que 1,6. Iste constatationes vale sin reguardo al etate del patiente. Le criterios electrocardiographic de allargamento atrial combinate—e le bases theoric de iste observationes—es etiam discutite.

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The exeretion of aldosterone and sodium was studied in 30 normal subjects and in 40 patients with various forms of heart failure before, during, and after treatment with digitalis, mercurials, and salt restriction. Healthy people consuming only 60 to 80 mEq. of sodium daily showed increased exeretion of aldosterone and decreased excretion of sodium. Nine of 12 untreated patients with severe hydropic heart disease due to combined "left-and right-sided heart failure" excreted moderately increased amounts of aldosterone and reduced amounts of sodium. After cardiac recompensation was re-established sodium and aldosterone exeretion was within normal limits. Seven of 8 patients with pulmonary congestion but without systemic symptoms excreted normal amounts of aldosterone, whereas 5 of 7 patients with "right-sided failure" showed moderate to excessive increases in aldosterone excretion. Increased aldosterone activity was also noted in cardiac cirrhosis following abdominal paracentesis and in the first week following myocardial infaretion.

Kurland

Response of Serum Lipids and Lipoproteins of Man to Beta-Sitosterol and Safflower Oil

A Long-Term Study

By JOHN W. FARQUHAR, M.D., AND MAURICE SOKOLOW, M.D.

Previous studies in man have indicated that administration of either plant sterols or unsaturated dietary fats causes decreases in certain serum lipids. This report presents the results of a long-term 7-phase study of the comparative effects of the single and combined administration of plant sterols (β-sitosterol) and a highly unsaturated vegetable oil (safflower oil) in 15 ambulatory subjects. The serum lipid changes observed indicate that both agents act on the same low-density lipoprotein fraction, that the changes produced by β-sitosterol and by safflower oil are similar in magnitude, but that the combination has a 55 per cent greater effect than either agent alone, that the mechanisms of action of these 2 agents probably differ, and that the action of the safflower oil is probably not due to the amount of sitosterol it contains.

THE dietary factors that affect serum lipid levels of man have recently aroused considerable interest. This interest has stemmed in part from evidence linking premature complications of atherosclerosis with elevations of certain serum lipids.[1, 2] Two major dietary factors, plant sterols (phytosterols) and vegetable oils, have received particular attention because of their known effect of lowering the serum lipids of man.[3, 4]

Plant sterols are similar in structure to cholesterol. They are widely distributed as constituents of certain types of plants and are present in variable concentration in vegetable oils. The most common plant sterol is β-sitosterol; this substance significantly lowers the concentration of serum cholesterol when given to human subjects.[3, 5-7] A previous study[7] demonstrated that β-sitosterol not only lowers the concentration of total serum cholesterol but also reduces the level of total β-lipoprotein, although it has little effect on α-lipoprotein. In addition, β-sitosterol decreases the intestinal absorption of cholesterol.[8] It seems likely that the altered absorption is responsible for the changes in serum lipids, although the intermediate steps are not completely understood.

Vegetable oils of diverse composition, when substituted for the animal fats of the diet, have also been shown to lower serum cholesterol and β-lipoprotein cholesterol of man.[4, 9-15] There is disagreement, however, regarding the constituents of vegetable oils responsible for these effects.

Ahrens and associates,[4] in a recent summary of their data, found that the degree of unsaturation of a wide variety of dietary fats correlated with the extent of fall in the serum cholesterol concentration after their ingestion. On the other hand, Keys and coworkers[13] concluded that some factor other than the type or total amount of unsaturated fatty acid is responsible for part of the action of one vegetable oil (corn oil) on serum cholesterol of man. Recently, Beveridge and his associates[15] suggested that much of the effect of corn oil on serum lipids can be explained on the basis of its content of β-sitosterol.

The purpose of the present study was to investigate the effects of β-sitosterol and a particular vegetable oil (safflower oil), alone and in combination, on serum lipid concentrations of a group of 15 subjects. The same 15 were studied throughout to allow more accurate evaluation of the dietary factors under study. Safflower oil was chosen because

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its unique composition (high content of linoleic acid and virtual absence of β-sitosterol, tocopherol, and linolenic acid) would lessen some of the experimental variables observed with other vegetable oils. Various internal controls were included in an attempt to clarify other points in question, such as the magnitude of the effects of the agents studied, the rapidity and consistency of the fall and subsequent rise in serum lipid concentrations, and the stability of the changes observed. To define more accurately the lipoprotein changes that occur after administration of these agents, the concentration of the following serum lipids were measured: total cholesterol, α- and β-lipoprotein cholesterol, phospholipid, total lipid, and triglyceride.

Materials and Methods

Selection of Subjects

Fifteen ambulatory, nondiabetic subjects (14 men, 1 woman), averaging 48 years of age (range 36 to 63) were studied. Thirteen had been diagnosed clinically as having either arteriosclerotic heart disease or arteriosclerosis obliterans, 1 had no apparent disease, and 1 had mild hypertension. In 3 individuals xanthelasma was present; no xanthomatous lesions were noted in the other 12 subjects. The subjects were selected on the basis of intelligence, desire to cooperate, and ambulatory status. All knew they were participating in a research project and agreed to the scheduled weekly interviews.

Controls of Diet, Body Weight, and Activity

The habitual diet of each subject was determined in detail prior to starting the study. This diet, with slight modifications if needed to maintain constant body weight, was adhered to during all control and sitosterol test periods. The average composition of the diets was 2380 total calories (range 1961 to 3000): 41 per cent of the calories were derived from fat, (range 33 to 53 per cent), of which 95 per cent was animal or solid vegetable fat.

The daily cholesterol intake* averaged 0.62 Gm. daily (range 0.26 to 0.96) during the control and sitosterol test periods. To maintain similar daily cholesterol intakes during the safflower oil test period each subject consumed from 3 to 7 eggs weekly; the cholesterol intake during this period averaged 80 per cent of that during the other periods.

*Calculated from Cholesterol Content of Food. J. Am. Dietetic Assoc. 21: 341, 1954, by Ruth Okey.

Table 1.—*Composition of Safflower Oil**

	Edible (degummed, deodorized)	Hydrogenated (degummed)
Fatty acid composition† Wt. % of total fatty acids		
Linoleic acid	*73*	none
95% as cis-cis isomer		
Linolenic acid	<0.05	none
Oleic acid	*21*	55.3
Total saturated	*6*	—
Free fatty acids (as oleic)	0.04	—
Conjugated dienes	0.82	—
Conjugated trienes	none	—
Iodine value (Wijs)	*143* (142–144)	49.7
Phospholipid, wt. % (lipid phosphorus × 25)	0.008	—
α-tocopherols, wt. %	0.059	—
Unsaponifiable material, wt. %	0.60	0.40
Sterol content,‡ wt. %		
Free	0.09	—
Total	0.15	—
Preservatives added, wt. %		
Propylgallate	0.01	—
Citric acid	0.01	—
Melting point		115 C.

* Analyses performed in the laboratories of Pacific Vegetable Oil Corporation, San Francisco, and Durkee Famous Foods, Berkeley. Values in italics are an average of many serial determinations. The range of these repeat determinations was narrow.

† Standard AOCS spectrophotometric analysis of KOH-isomerized oil and infrared spectroscopic methods.

‡ Determined by both digitonin and infrared spectroscopic methods.

Experimental Design

After a preliminary stabilization period the subjects underwent a consecutive 7-phase study, averaging 43 weeks in duration (range 35 to 54 weeks). The study was divided into 4 control periods of approximately 6 weeks each (phases I, III, V, and VII) alternated with 3 test periods (phases II, IV, and VI), averaging 8 weeks in duration (range 4 to 14 weeks).

In any study on the effect of multiple dietary variables on serum lipids, it is important to

TABLE 2.—*Average Body Weights (Kg.) of Subjects*

	Phases of the study—consecutive in time						
	I	II	III	IV	V	VI	VII
Mean*	72.9	72.9	72.9	72.8	73.0	72.9	72.8
S.D.†	±9.2	±8.8	±9.1	±9.4	±9.4	±9.6	±9.0

* Represents the mean of the average individual weights during period.

† Standard deviation $\frac{\sqrt{\Sigma (x-\bar{x})^2}}{n-1}$.

ensure that the agent given first in time does not affect the response to a subsequent agent. This objective was approached in our project by placing control periods between randomized test periods. This alternating design allowed close comparison of the lipid levels during the test and control phases.

During the control periods, the subjects consumed their habitual (control) diet, and in addition were given a placebo* similar in taste and consistency to the sitosterol preparation. During phases II and IV the subjects received either the control diet plus 18 Gm. (90 ml.) of β-sitosterol* daily, taken in 3 equal portions orally immediately before meals, or a total of 81 Gm. (90 ml.) of safflower oil daily, substituted for a computed equicaloric portion of the animal and solid vegetable fat of the control diet. The safflower oil was obtained from a single source,† and was stored at a temperature of less than 25 C. Frequent analyses performed during the study showed no changes in the composition of the oil (table 1). The oil was ingested in a variety of ways, most commonly as a suspension in skimmed milk or fruit juice, but also as an artificial ice cream or a salad oil. Use of the oil in frying or baking was forbidden. During phase VI the subjects received a combination of both β-sitosterol and safflower oil administered as in phases II and IV. In addition, 2 subjects were studied immediately after the safflower oil phase for an additional 2 weeks during which they ingested 81 Gm. of partially hydrogenated safflower oil daily (see table 1 for composition). A longer test period was not possible because of the relative unpalatability of the preparation.

Methods

During each phase serum was obtained from the subjects in the fasting state at weekly intervals. Each sample was analyzed for total cholesterol by the method of Abell et al.[18] and for α- and β-lipoprotein cholesterol (ALPC and BLPC) by a modification of the method of Anderson and Keys.[17] Our method differed chiefly in the technic of paper electrophoresis used for the initial separation. A brief description of our electrophoretic procedure follows: Six 33 cm. Whatman 3 MM paper strips (chromatography grade) were mounted in a vertical suspension electrophoresis apparatus similar to that described by Williams et al.[18] Serum, 0.04 ml., was applied to 3 strips 2.5 cm. in width, and 0.1 ml. was applied to 3 paired strips 6 cm. in width. Electrophoresis was performed for 15 hours at 5 C. in barbital buffer of pH 8.6 and ionic strength 0.05. After oven-drying on a horizontal rack for 30 minutes at 100 C., the narrow strips were stained with Sudan black-B. The wide strips were cut into 2 segments, corresponding to the α- and β-lipoprotein fractions that appeared on the stained strip. The segments of the unstained strip were then analyzed for total cholesterol by the method of Anderson and Keys.[17]

The coefficient of variation of differences* between 46 duplicates of total serum cholesterol in our laboratory was ± 1.2 per cent. Ninety replicates were analyzed for total serum cholesterol at intervals after storage of the serum in the frozen state for 1 to 12 months after the initial analysis. The coefficient of variation of these replicates was ± 3.1 per cent. The sum of ALPC and BLPC averaged 97.5 per cent of the total serum cholesterol, and represents the degree of recovery of cholesterol from the paper. The coefficient of variation of differences between 129 duplicates of total serum lipid was ± 1.1 per cent; for 133 duplicates of total serum phospholipid this value was ± 0.8 per cent.

Aliquots of each individual's serum samples were pooled for each phase and analyzed for total lipid by the method of Bragdon[19] and for lipid phosphorus by the method of Stewart and Hendry.[20] The factor 1.68 was used to convert ester cholesterol to cholesterol ester, a constant ratio of 0.27 was assumed for free to total cholesterol, and phospholipid was calculated from lipid phosphorus by use of the factor 25. Serum triglycerides were calculated by the method of Bragdon.[19]

RESULTS

The subjects' body weights in all phases and the serum lipid levels during the control phases served as internal experimental controls.

*The placebo and the β-sitosterol (Cytellin) were generously supplied by the Eli Lilly Company, Indianapolis, Ind., courtesy of Drs. Robert Shipley and Kenneth Kohlstaedt.

†Purchased from the Pacific Vegetable Oil Corporation, San Francisco, Calif.

*Coefficient of variation = standard deviation of differences between duplicates divided by mean difference × 100 per cent.

TABLE 3.—*Summary of Mean Serum Lipid Changes During the Test and Control Phases*

Serum lipid fraction mg./100 ml.	Control*	β-sitosterol	Safflower oil	β-sitosterol and safflower oil
Total cholesterol	279 ± 43†	*233* ± 38	*233* ± 33	*204* ± 33
β-lipoprotein cholesterol	233 ± 42	*186* ± 41	*185* ± 32	*157* ± 33
α-lipoprotein cholesterol	40 ± 10	40 ± 13	42 ± 10	42 ± 13
Phospholipid‡	279 ± 30	*248* ± 30	*252* ± 42	*239* ± 23
Total lipid‡	831 ± 106	*711* ± 114	*700* ± 112	*652* ± 98
Triglyceride‡	141 ± 46	124 ± 68	109 ± 51	119 ± 53
Cholesterol: phospholipid	1.00	0.94	0.93	0.84

* Derived from average of all control periods.
† Mean ± standard deviation.
‡ Derived from pooled samples.
Values in italics differ from control significantly ($p < 0.01$).

Body Weight

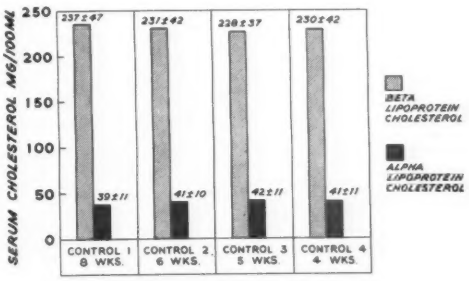
The maximum difference in the average weights of all subjects between any 2 phases was less than 1 per cent (table 2). Individual weights were also closely maintained; none of the subjects had a weight change of more than 3.5 Kg., and 9 subjects had a change of less than 2.0 Kg. during the entire study.

Serum Lipid Concentrations

The first 2 weeks of each phase were required for stabilization of the serum lipid concentrations. Consequently, the figures for these periods were not included in the calculations of the average control and test values.

During Control Periods. The average serum lipid values for the control periods, phases I, III, V, and VII, were analyzed separately (fig. 1); the results served as one check on the consistency of the return of the subjects to their control diets. As shown in figure 1 the average total serum cholesterol and the ALPC and BLPC levels were remarkably stable during all control periods. The maximum average difference in these serum lipid levels between any of the 4 phases was less than 4 per cent.

During Test Periods. A prompt and sustained fall in the concentration of serum total lipid, phospholipid, and BLPC occurred in all subjects during test phases II, IV, and VI (table 3). All the decreases were statistically significant ($p = < 0.01$) when analyzed by a 2-way classification analysis of variance.[21] No significant change in the level of ALPC was found during these phases,



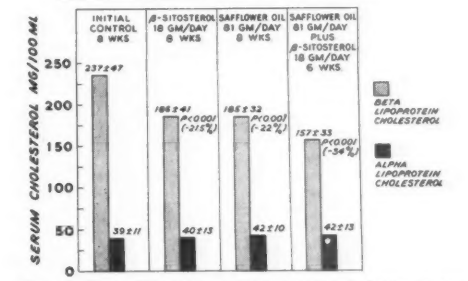


FIG. 1 *Top.* The serum lipoprotein cholesterol concentrations of the entire group (15 subjects) during the 4 control periods of the study. The maximum average difference between periods was 4 per cent. Values are recorded as mean ± standard deviation.

FIG. 2 *Bottom.* The effect of β-sitosterol and safflower oil on the serum lipoprotein cholesterol concentrations of the entire group of 15 subjects. The values are recorded as mean ± standard deviation. The differences were analyzed by a method of a 2-way classification of variance.

and serum triglyceride levels, although slightly decreased, did not differ significantly from the control levels ($p = > 0.05$). However, since the triglycerides were calculated from each of the other 3 lipid moieties measured and a summation of errors may

TABLE 4.—*Changes in β-Lipoprotein Cholesterol Concentrations in Each Phase of Study*

Subject	Phase of the study*			
	Control†	Sitosterol	Safflower oil	Combination
OB	244 ± 11‡	189 ± 6	185 ± 21	175 ± 6
WB	235 ± 7	180 ± 5	192 ± 13	153 ± 6
HC	265 ± 10	212 ± 13	221 ± 14	199 ± 10
MC	221 ± 13	183 ± 9	152 ± 6	126 ± 3
GD	193 ± 10	145 ± 11	158 ± 16	138 ± 7
RE	206 ± 13	162 ± 6	147 ± 11	122 ± 3
HF	212 ± 21	158 ± 7	181 ± 10	156 ± 13
WL	196 ± 10	171 ± 12	167 ± 4	149 ± 7
FP	281 ± 21	237 ± 15	228 ± 6	187 ± 10
RP	213 ± 13	166 ± 11	185 ± 5	130 ± 9
RS	332 ± 30	264 ± 9	225 ± 22	195 ± 6
HS	224 ± 11	195 ± 15	215 ± 12	180 ± 7
HV	171 ± 20	139 ± 13	124 ± 9	95 ± 7
CW	217 ± 10	154 ± 11	169 ± 11	135 ± 10
JW	280 ± 22	229 ± 8	220 ± 18	207 ± 11

* Mean number of determinations per phase: control, 18; sitosterol, 7; safflower oil, 7; combination, 5.
† Mean of all control samples of each of the 4 control periods.
‡ Mean ± standard deviation.

occur in such calculations. the reliability of this measurement is reduced.

Although individual differences did occur, the average reductions in concentration of BLPC during the β-sitosterol and safflower oil phases were almost identical: 51 mg. (standard error of mean difference = ± 3.13) and 52 mg. per 100 ml. (standard error of mean difference = ± 5.82), respectively. Table 4 lists the BLPC values for each individual for all phases of the study. The average reduction in BLPC levels during administration of β-sitosterol and safflower oil combined was 80 mg. per 100 ml. (standard error of mean difference = ± 9.84), a 55 per cent greater decrease than that observed when either agent was given alone (fig. 2). The average reduction in BLPC concentration from control levels for the sitosterol, safflower oil, and combination phases was 22, 22, and 34 per cent, respectively.

Changes in serum cholesterol fractions (BLPC and ALPC) of 2 representative subjects are depicted in figure 3.

The 2 subjects who were given hydrogenated safflower oil for a 2-week period at the termination of the safflower oil phase showed a rise in serum BLPC concentration. This increase was from 165 mg. to 180 mg. per 100 ml. in 1 individual, and from 170 mg. to 205 mg. per 100 ml. in the second individual. A further rise in BLPC concentration occurred after return to the control diet (from 180 mg. to 204 mg. per 100 ml. and from 205 mg. to 222 mg. per 100 ml., respectively).

Rate and Magnitude of Change in Serum Lipid Levels

The fall in serum lipid levels during each test phase and their rise during the subsequent control phase were comparable in rate. All changes were rapid, taking place during the first 2 weeks of each phase, after which they leveled off and remained stable.

Comparison of the BLPC levels at weekly intervals showed that the maximum effect occurred during the first week of each phase. The reduction in concentration during both the sitosterol and safflower oil phases averaged 50 mg. per 100 ml.; the magnitude of these reductions at the end of the first week was 49 mg. and 34 mg. per 100 ml., respectively (fig. 4). The difference between the means of these 1-week values was statistically significant ($p = < 0.01$). The rate of rise during the control period paralleled the rate of fall during the preceding test period, i.e.,

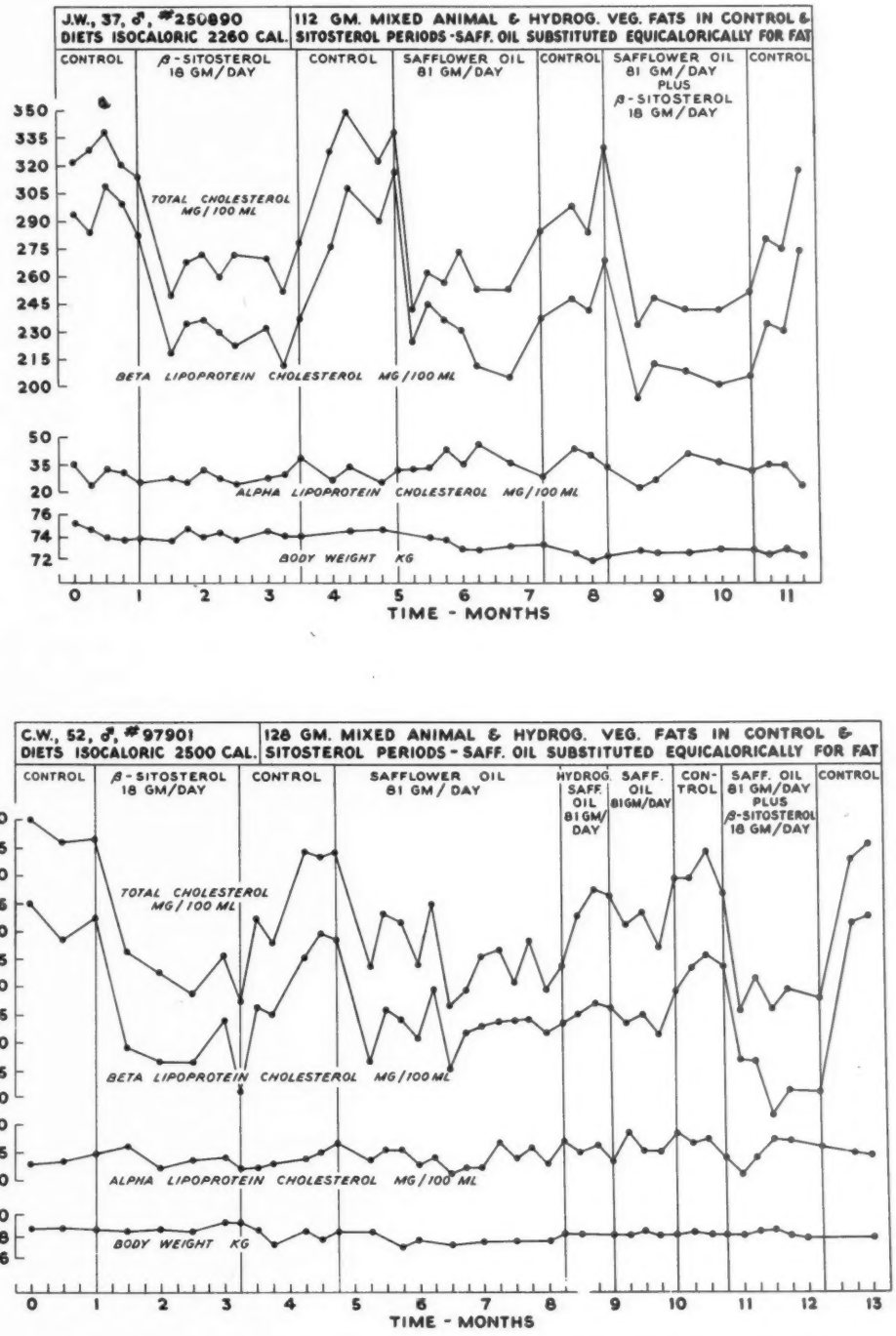


FIG. 3. A comparison of the response of serum lipoprotein cholesterol concentrations in each of 2 patients.

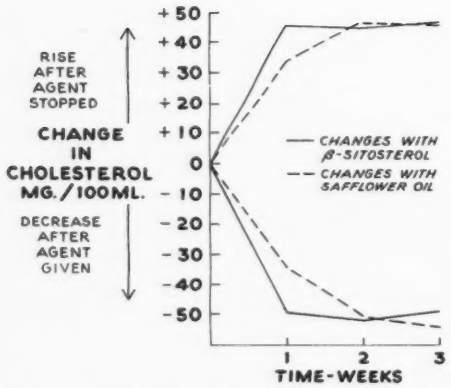


FIG. 4. Illustration of the delayed action of safflower oil compared to β-sitosterol. The solid line represents the changes with β-sitosterol, the dotted line the changes with safflower oil. The data are derived from 11 of the 15 subjects.

the rise was somewhat slower after cessation of safflower oil than after sitosterol (fig. 4). The average reduction in concentration of BLPC during the combination phase was 80 mg. per 100 ml.; the amount of this fall at the end of the first week was 50 mg. per 100 ml. Again, the rate of return to control levels paralleled the rate of decrease during the test phase.

Clinical Data

All agents were well tolerated by the subjects, and no abnormal clinical signs or symptoms developed during the course of the experiment. There was no definite change in the frequency of the angina pectoris; in some subjects the exercise tolerance appeared to be greater. Photographs of the 3 subjects with xanthelasma taken at the beginning and end of the study showed a reduction in the size of the lesion in only 1 case.

DISCUSSION

Ingestion of β-sitosterol resulted unequivocally in a prompt and significant fall in serum cholesterol in our subjects. The rate, magnitude, and stability of this decrease and the subsequent return to control values paralleled the results in a previous study on a different group of subjects.[7]

The lipoprotein fraction affected during all 3 experimental periods appeared to consist exclusively of low-density (or beta) lipoproteins, since ALPC concentrations remained unchanged. On the basis of the known chemical composition of the various low-density lipoprotein classes and the distribution of cholesterol among them, it is evident that the lipoprotein fraction affected during all 3 experimental phases was predominantly S_f 0-10.[21, 22]

The mechanisms by which serum cholesterol is lowered after ingestion of sitosterol in man are by no means clear. Hernandez and Chaikoff[8] have shown that sitosterols decrease gastrointestinal absorption of C^{14} cholesterol in the rat; furthermore, experiments in man have demonstrated that sitosterols are poorly absorbed from the intestine.[23] Since hepatic synthesis of cholesterol apparently can compensate for alterations in dietary cholesterol in the rat,[24] it appears unlikely that sitosterol could lower the concentration of cholesterol in the serum simply by inhibiting its absorption. However, even if a similar hepatic control existed in man, the resultant compensation might not be sufficient to prevent sitosterol from inducing a temporary state of negative cholesterol balance. After re-establishment of a steady state, total body cholesterol might remain significantly reduced, and this reduction could be manifested by a decrease in the cholesterol content of the serum.

The recent experiments of Beveridge and associates[25] indicate that as little as 1.5 Gm. of β-sitosterol daily will appreciably reduce serum cholesterol concentrations in human subjects ingesting a fat-free, cholesterol-free formula diet. These observations suggest that the action of sitosterol on endogenous cholesterol reabsorption is important and that the presence of relatively small amounts of these sterols in the diet of various peoples may influence their serum cholesterol concentrations.

In our study administration of safflower oil in a constant amount of 81 Gm. daily (supplying from 24 to 37 per cent of total calories, average 31 per cent) to ambulatory subjects consuming nonformula diets lowered certain β-lipoprotein cholesterol concentra-

tions for periods up to 14 weeks. This decrease might have been caused simply by omission from the diet of animal and hydrogenated vegetable fat. Alternatively, the substituted vegetable oil itself could have been responsible, or both factors might have been involved. It is unlikely that the action of safflower oil is dependent on sitosterol, linolenic acid, or tocopherol (because of their low concentration in the oil), although it might be related to linoleic acid, which is present in high concentration. The rise in BLPC levels in 2 of our subjects after administration of linoleic acid-free hydrogenated safflower oil would support the assumption that serum cholesterol concentration is at least partly dependent on the degree of unsaturation of dietary fats. Since the observations on the action of hydrogenated safflower oil were limited in scope, further conclusions are not warranted.

The somewhat slower change in BLPC levels during and after administration of safflower oil than during and after β-sitosterol suggests that the 2 compounds differ in mechanism of action. It seems very unlikely that the 50 per cent greater decrease in serum cholesterol effected by the 2 agents combined results from the added action of the small amount of sitosterol present in safflower oil (approximately 0.12 Gm. per 81 Gm.), particularly since the effects of ingesting 9 Gm. and 18 Gm. of sitosterol daily are similar in magnitude.[7]

Investigation of the effects of ingestion of pure fatty acids to which varying amounts of sitosterol can be added might aid in clarifying the role of sitosterol in the action of vegetable oils. Such studies are in progress. Since it is possible that the unsaturated fatty acid portion and the plant sterol fraction of plant oils will be found to have independent hypocholesterolemic actions, the effect of these agents on fecal cholesterol balance will also be studied.

Summary

Fifteen ambulatory subjects with clinical evidence of atherosclerosis were studied during a 7-phase experiment lasting 35 to 54 weeks. They were given in random sequence β-sitosterol, 18 Gm. per day in conjunction with the control diet which contained 39 per cent of calories derived from animal or hydrogenated vegetable fat; safflower oil, 81 Gm. per day as 31 per cent of total calories in equicaloric substitution for animal and hydrogenated vegetable fat of the control diet; and a combination of the 2. Placebos were administered during the control period that preceded and followed each test period. Serum lipids were measured weekly.

A rapid and sustained fall in β-lipoprotein cholesterol (BLPC), total lipid and phospholipid occurred during each of the 3 test periods. The average fall in BLPC after ingestion of the test agents was: sitosterol alone, 22 per cent; safflower oil alone, 22 per cent; the 2 combined, 34 per cent. Average body weights were constant during the study, and the average serum cholesterol concentrations were closely similar during the 4 control periods. The uniformity of serum lipid response to the test agents, coupled with the stability of average body weights and control BLPC concentrations, indicates that confidence can be placed in the results of long-term dietary studies using nonformula diets in well-instructed ambulatory subjects.

The fall and subsequent rise in BLPC were more rapid with sitosterol than with safflower oil, suggesting that the 2 agents have different mechanisms of action. The 55 per cent greater fall in BLPC after ingestion of sitosterol and safflower oil combined indicates that the action of safflower oil is not likely to be the result of the small amount of sitosterol it contains. Other possible explanations for the changes observed with safflower oil are discussed.

Since no significant changes in alpha lipoprotein cholesterol or triglyceride were observed during the study, it was concluded that the S_f 0-10 fraction of the serum β-lipoproteins was primarily affected by the test agents.

Acknowledgment

The authors wish to express their appreciation to Dr. Richard J. Havel for helpful suggestions given during the course of the study and to Dr.

Calvin Zippin for assistance in the statistical methods. We also wish to thank Miss H. Madigan for aid in preparing the dietary aspects and Mrs. J. Moore and Miss R. Zanow for technical assistance.

SUMMARIO IN INTERLINGUA

Dece-cinque subjectos ambulatori con signos clinic de atherosclerosis esseva studiate in un experimento heptiphasic de un duration de 35 a 54 septimanas. Omne le subjectos esseva studiate durante tres periodos experimental e quatro periodos de controlo ante, inter, e post le periodos experimental. Durante le periodos experimental illes recipeva (1) sitosterol beta, 18 g per die, in conjunction con le dieta de controlo que contineva grassia animal o hydrogenate grassia vegetal amontante a 39 pro cento del valor caloric, (2) oleo de carthamo, 81 g per die, representante 31 pro cento del total ingestion caloric e reimplaciante un quantitate equicaloric de grassia animal o de hydrogenate grassia vegetal in le dieta de controlo, e (3) un combination del 2. Le ordine del periodos correspondente a iste 3 dietas experimental variava al hasardo inter le 15 subjectos. Supplementos fictitie esseva administrate durante le 4 periodos de controlo. Le lipidos seral esseva mesurate septimanalmente.

Un rapide e sustenite reduction del cholesterol de lipoproteina beta (CLPB), del lipido total, e del phospholipido occurreva durante cata un del 3 periodos experimental. Le reduction medie de CLPB post le ingestion del agentes experimental esseva 22 pro cento post sitosterol sol, 22 pro cento post oleo de carthamo sol, e 34 pro cento post le combination del 2. Le pesos corporee medie esseva constante durante le studio, e le concentrationes medie del cholesterol seral esseva multo simile durante le 4 periodos de controlo. Le uniformitate del responsa sero-lipidic al agentes experimental, insimul con le stabilitate del pesos corporee medie e del concentration de CLPB de controlo, indica que il es justificate haber confidentia in le resultatos de studios dietari a longe vista con dietas altere que per formula alimentari, providite que le subjectos (qui pote esser ambulatori) es ben instruite.

Le reduction e le subsequente re-augmento de CLPB esseva plus rapide con sitosterol que con oleo de carthamo. Isto pare indicar que le 2 agentes ha differente mechanismos de action. Le facto que le reduction de CLPB esseva 55 pro cento plus grande post le ingestion de sitosterol e de oleo de carthamo in combination indica que le action de oleo de carthamo non se explica facilemente per le presentia de micre quantitates de sitosterol in illo. Explicationes plus probabile del alterationes observate con oleo de carthamo es discutite.

Viste le facto que nulle alterationes significative de cholesterol de lipoproteina alpha o de triglycerido esseva observate durante le studio, il esseva concludite que le agentes experimental afficeva primarimente le fraction S_f 0-10 del lipoproteinas beta in le sero.

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Five different spectra of proteins were found by paper electrophoresis in the urine of patients with congestive heart failure. All contained albumin, only exceptionally isolated, usually in combination with 1 to 3 globulin fractions, the most common being alpha and beta globulin. Gamma globulins were found in protein-rich urines but also with low protein concentrations following ultrafiltration, suggesting a renal factor contributing to proteinuria in heart failure. The authors believe that the various spectra of globulin fractions may have different prognostic significance.

Pick

Radioiodine Treatment of Paroxysmal Supraventricular Tachycardia in the Euthyroid Patient

By Eliot Corday, M.D., Herbert Gold, M.D., and Henry L. Jaffe, M.D.

Twenty-five euthyroid patients subject to recurrent paroxysmal supraventricular tachycardias, which were resistant to usual prophylactic therapy, were treated with radioactive iodine. In many of the patients, with follow-up ranging up to 6 years, there were no recurrences of the tachycardia subsequent to the isotope therapy. Two patients were considered refractory to this therapy.

IN THE euthyroid patient, rapid supraventricular tachycardias occur and are often resistant to prophylactic treatment with quinidine or pronestyl.[1] In an attempt to evaluate the effect of radioactive iodine in cases of supraventricular tachycardia resistant to antiarrhythmic drugs, the authors treated 25 such patients with radioactive iodine and observed them for periods up to 6 years.[2] In all instances prophylactic treatment with antiarrhythmic drugs had failed to prevent recurrent attacks. Twenty-two of these patients had arteriosclerotic heart disease and 3 had rheumatic heart disease. Many of the patients had recurrent attacks as often as 4 times a day. In many instances, during the paroxysm of tachycardia, the patient suffered severe anginal discomfort. All patients were considered euthyroid on the basis of clinical examination by 3 physicians and normal laboratory findings, including serum protein-bound iodine and radioactive iodine uptake.

The patients with arteriosclerotic heart disease were selected from private practice. In these patients, the clinical history and the resting electrocardiogram or Master 2-step test revealed indications of coronary artery disease. The 3 patients with rheumatic heart disease all had multivalvular disease. The electrocardiographs during the episodes of tachycardia revealed supraventricular rhythms, either paroxysmal atrial tachycardia, nodal tachycardia, or atrial fibrillation.

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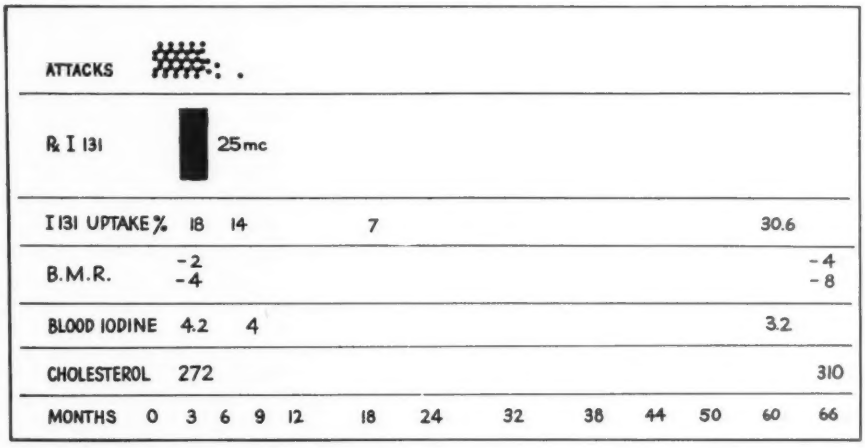
Classification of Results

The results of treatment with radioactive iodine were classified as good, fair, or poor. A result was considered good when no recurrences or very few paroxysms of tachycardia occurred following the period of treatment. A result was classified as fair when there were no or very few paroxysms for 12 months after the period of treatment following which time there were occasional recurrences. A poor result was one in which radioactive iodine failed to affect the frequency of paroxysms.

Methods and Material

Treatment. We prefer to give oral doses of 6 mc. (millicuries) of radioactive iodine at weekly intervals until the patient has received a total of 25 to 30 mc.[3] We have chosen the small dose technic to avoid the danger of suddenly releasing large amounts of thyroxin into the blood stream from the gland.[3] This could produce a temporary increase in metabolism which, in a severely ill cardiac patient, might be detrimental. It usually took 2 to 3 months following treatment for the radioactive iodine to reach maximum hypometabolic levels. This is considered the usual period of treatment. However, some patients required a further course of I^{131} treatment adequately to depress thyroid function. Although our purpose was to induce a state of only relative hypothyroidism, occasionally some of our patients developed clinical myxedema. Four of the 25 patients became myxedematous following I^{131} therapy. This was corrected by the administration of thyroid in doses varying from 6 mg. to 45 mg. a day. All of the patients were comfortable and had few or no complaints as a result of the reduced thyroid function.

Medical Management Following Radiation. During the period of treatment, which usually lasted



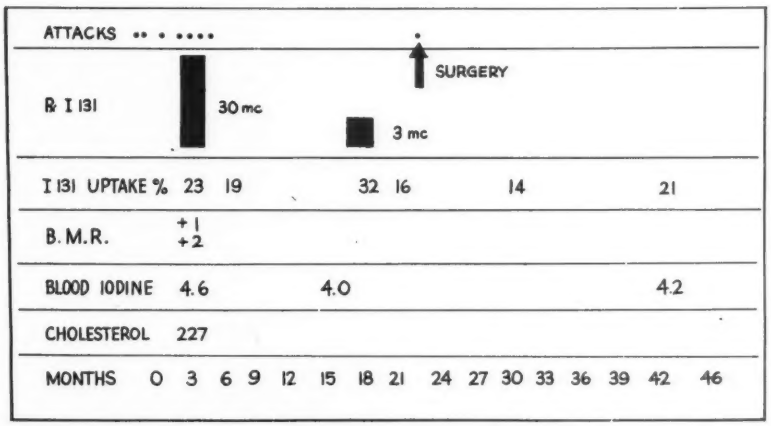


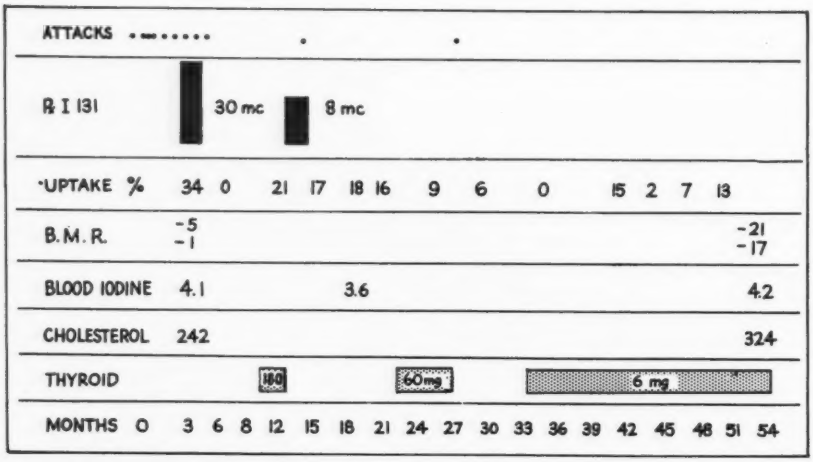
FIG. 1 *Top.* Clinical course of case 1, euthyroid patient treated with radioactive iodine for recurrent attacks of atrial tachycardia. Note that there have been no recurrences of the tachycardia in the last 61 months. This is a good result.

FIG. 2 *Bottom.* Graph of case 2 showing clinical course following treatment with radioactive iodine for recurrent episodes of atrial tachycardia. Note that there was only 1 episode of tachycardia in a 46-month period and this was precipitated by a gastrectomy. This is a good result.

from 8 to 12 weeks, the patients were asked to curb their physical and emotional activities. Following the period of treatment, the patients were examined for signs of myxedema, such as coldness, lacrimation, joint pain, muscle pain, lethargy, weight gain, edema of eyelids, swelling of submaxillary glands, dry skin, and cardiac enlargement. As soon as any sign of myxedema occurred, the patient was given 6 mg. of thyroid daily in the morning. If the early signs of myxedema did not subside within 2 weeks, the same dosage of thyroid was administered 2 or 3 times a day.

Case Reports. Reports of cases showing good, fair, and poor results of treatment with radioactive iodine follow.

Case 1 (fig. 1). A 54-year-old man had severe coronary artery disease and paroxysms of nodal tachycardia that occurred once or twice a day. They usually awakened him from sleep in the early morning hours. During the tachycardia, he experienced severe precordial pain radiating down the left arm. The patient also stated that heavy physical exertion, such as walking quickly, caused



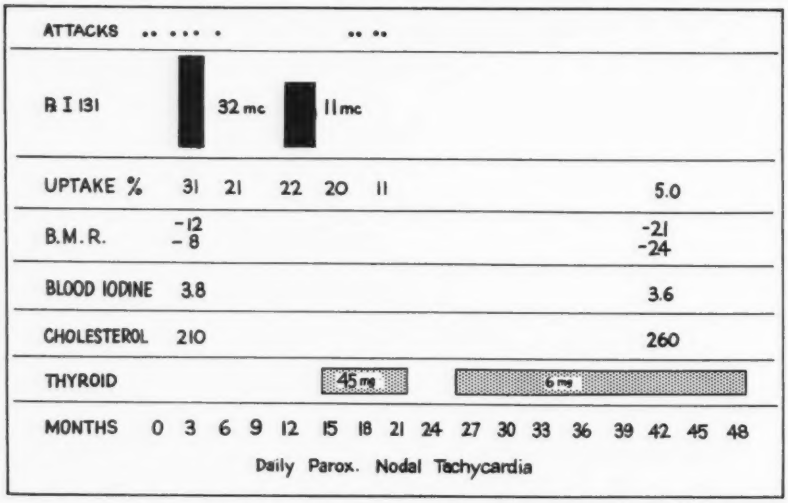


FIG. 3 *Top.* Clinical course of case 3. Prior to treatment with I^{131} this patient had recurrent episodes of atrial tachycardia every 2 weeks. Following treatment, she has had but 2 episodes in a 51-month period. This is a good result.

FIG. 4 *Bottom.* Clinical course of case 4 showing a fair result following treatment with radioactive iodine. Attacks were induced by overmedication with thyroid extract.

similar pain. The resting electrocardiogram was normal; however, nodal tachycardia with marked S-T segment depression occurred following exercise for the Master 2-step test. Roentgenograms of the chest demonstrated no cardiac enlargement. The basal metabolic rate was –4 per cent, protein-bound iodine was 4.2 meg. per 100 ml., and blood cholesterol was 272 mg. per cent. The 24-hour I^{131} uptake was 18 per cent. The patient was given 25 mc. of radioactive iodine in divided doses in a 4-week period. The attacks then lessened in frequency over a period of 3 months following the treatment with radioactive iodine. In the fourth month, the patient had only 1 further severe attack of nodal tachycardia, at which time the 24-hour I^{131} uptake was 14 per cent and the protein-bound iodine, 4.0 meg. per 100 ml. In the last 61 months, the patient has experienced no attacks of tachycardia. Recent basal metabolic rate was —4 per cent, protein-bound iodine, 3.2 meg. per 100 ml., blood cholesterol 310 mg. per cent; and 24-hour I^{131} uptake 30.6 per cent. The result was classified as good in this patient followed for 66 months.

Case 2 (fig. 2). A 48-year-old woman suffered recurrent attacks of atrial tachycardia every second or third month, which lasted for 3 to 4 hours. These attacks were not relieved by carotid sinus massage or other maneuvers, but appeared to respond to intravenous Cedilanid 3 hours following its administration. The patient experienced severe precordial pain within a half hour following the onset of the attack of tachycardia, which radiated down the left arm and into the left side of the jaw. During the paroxysms she became dyspneic. Physical examination during a free interval showed the heart to be normal in size and no murmurs were present; the blood presure was 118/80 mm. Hg. The skin was dry and there were no signs of thyrotoxicosis. X-ray examination of the chest showed no abnormalities. The Master 2-step test was positive. The basal metabolic rate was +1 per cent, protein-bound iodine was 4.6 mcg. per 100 ml.; and blood cholesterol was 227 mg. per cent. The 24-hour I^{131} uptake was 23 per cent. The patient was given Pronestyl and Quinidine, but these drugs failed to prevent recurrent episodes of tachycardia. She was then given 30 mc. of radioactive iodine in divided weekly doses. The paroxysms recurred 4 times over a 9-week period and then ceased. The 24-hour I^{131} uptake was 19 per cent. Eighteen months after treatment with radioactive iodine, her 24-hour I^{131} uptake was 32 per cent. Although she was asymptomatic, she was given another 3 mc. of radioactive iodine. At the twenty-first month after the original treatment, the 24-hour I^{131} uptake was 16 per cent. Twenty-four months after the treatment with radioactive iodine a carcinoma of the fundus of the stomach was removed by a gastrectomy. On the third postoperative day, a paroxysm of atrial tachycardia occurred which stopped 2 hours after Cedilanid was administered intravenously. The patient, however, did not experience any precordial distress during this paroxysm. For 22 months since this last attack there has been no recurrence. The 24-hour I^{131} uptake at the thirtieth month was 14 per cent and then at the forty-second month was 21 per cent. The protein-bound iodine was 4.2 mcg. per 100 ml. The results were classified as good in this patient followed for 46 months.

Case 3 (fig. 3). A 51-year-old woman complained of severe "racing spells" of the heart due to paroxymal atrial tachycardia which occurred every second or third week. Shortly after the onset of these attacks she developed severe precordial pain radiating to the left arm, associated with choking sensations. Examination revealed a rather obese woman of 170 lb. with a dry skin and no evidence of thyrotoxicosis. The heart was normal in size and there were no murmurs. The resting electrocardiogram was normal. However, the Master 2-step test was considered positive. The basal metabolic rate was –5 per cent, protein-bound iodine was 4.1 mcg. per 100 ml., and blood cholesterol was 242 mg. per cent. The 24-hour I^{131} uptake was 34 per cent. She was given 30 mc. of radioactive iodine in divided weekly doses. The paroxysms of atrial tachycardia continued for a 13-week period and then ceased. Twelve months following treatment with radioactive iodine, she experienced an episode of palpitation and an electrocardiogram revealed supraventricular tachycardia. However, at this time she did not notice any chest discomfort except for rapid heart action. It was then discovered that the patient had been taking 180 mg. of thyroid daily on her own initiative in an attempt to reduce her weight and this drug was discontinued. Her 24-hour I^{131} uptake was 21 per cent. She was given another 8 mc. of radioactive iodine. No further episodes of tachycardia occurred until the twenty-seventh month following treatment, at which time she had a short paroxysm of tachycardia, but again did not experience any precordial pain. At this time she was taking 60 mg. of thyroid, self-prescribed. The 24-hour I^{131} uptake was 6 per cent. Therefore, she was not given any additional treatment with radioactive iodine. During a further 27-month period she has not developed any more episodes of tachycardia. Her basal metabolic rate at this time was –21 per cent; protein-bound iodine was 4.2 mcg. per 100 ml.; and blood cholesterol was 324 mg. per cent. The 24-hour I^{131} uptake was 13 per cent. The result was considered good in this patient followed for 54 months.

Case 4 (fig. 4). A woman 55 years of age had sustained several attacks of coronary thrombosis. In addition, attacks of paroxysmal atrial tachycardia occurred every 3 to 4 months. Prior to treatment with radioactive iodine, she was admitted to the hospital on 4 occasions in a 6-month period because of severe angina associated with the tachycardia. The patient was markedly obese. Her weight was 172 lb. The heart sounds were normal. Roentgenogram of the chest revealed a normal size heart and clear lung fields. The electrocardiogram showed an old myocardial infarction. The basal metabolic rate was –12 per cent, protein-bound iodine 3.8 mcg. per 100 ml.; and blood cholesterol was 210 mg. per cent. The 24-hour I^{131} uptake was 31 per cent. Because of the severe angina resulting from the recurrent attacks of tachycardia, which could not be controlled with antiarrhythmic drugs, the patient was given 32 mc. of radioactive iodine in divided weekly doses. She had 3 further attacks, 3, 20, and 54 days following treatment. Twelve months following the initial dose, her 24-hour I^{131} uptake was 22 per cent. She was then given another 11 mc. of radio-

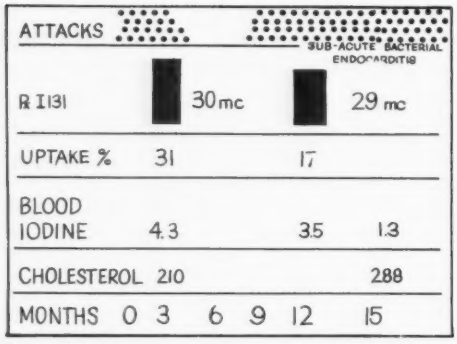


FIG. 5. Graph demonstrating the clinical course of case 5 in which the results were classified as poor.

active iodine. No further episodes of tachycardia occurred until the fifteenth month following treatment. The 24-hour I^{131} uptake at the 15th month was 20 per cent. The patient then developed evidence of hypothyroidism. She was therefore given 45 mg. of thyroid per day in divided doses for a 7-month period. Subsequently, in the eighteenth month she developed 1 paroxysm of tachycardia. In the nineteenth month she experienced a very severe episode of tachycardia, which was converted to sinus rhythm by intravenous Cedilanid. This attack was associated with severe precordial pain. Her 24-hour I^{131} uptake shortly after this episode was 11 per cent. Following the news of the death of her father, 22 months after the first treatment with radioactive iodine, she again experienced a severe episode of tachycardia and another episode 1 month later. During the next 21 months the dosage of thyroid was reduced from 45 to 6 mg. daily and she had no further episodes of tachycardia. Forty-two months after treatment, her basal metabolic rate was −24 per cent, protein-bound iodine was 3.6 meg. per 100 ml., and blood cholesterol was 260 mg. per cent. The 24-hour I^{131} uptake was 5.0 per cent. Because the patient had experienced 5 episodes of tachycardia in the 48 months following tratment with radioactive iodine, the result was classified as fair. The probable reason for the recurrences of the tachycardia was the ingestion of excessive thyroid medication.

Case 5 (fig. 5). A woman 61 years of age with rheumatic heart disease developed paroxysmal atrial fibrillation every third or fourth week. There was a rumbling diastolic apical murmur and other findings indicating mitral valvular disease. Clinically her appearance was that of hypothyroidism. The protein-bound iodine was 4.3 meg. per 100 ml., and the blood cholesterol was 210 mg. per cent. The 24-hour I^{131} uptake was 31 per cent. She was given 30 mc. of radioactive iodine in divided weekly doses. Following the period of administration of this treatment, no further episodes occurred for a 4-month period. At this time, because of marked improvement in her cardiac condition, hysterectomy could be done. Following this procedure, the patient developed a menopausal psychosis. The 24-hour I^{131} uptake at this time was 17 per cent, and the protein-bound iodine was 3.5 meg. per 100 ml. Paroxysms then recurred almost daily. An additional radioactive iodine treatment of 29 mc. was therefore given and the attacks continued. At the end of the fifteenth month the protein-bound iodine was 1.3 meg. per 100 ml., and the blood cholesterol was 288 mg. per cent. In this patient the result was classified as poor. She was subsequently readmitted to the Cedars of Lebanon Hospital Clinic with subacute bacterial endocarditis and had chronic atrial fibrillation.

RESULTS

A total of 25 patients were treated with radioactive iodine. Of these, 20 had a good result, 17 patients had no paroxysms of arrhythmia, and 3 had an occasional paroxysm following treatment with radioactive iodine. However, in these latter patients, the paroxysms were induced by surgery or the ingestion of excessive thyroid.

Three other patients had a fair result, viz., no recurrence of tachycardia after treatment for periods of 12 to 14 months, but following this period, they experienced occasional episodes of tachycardia, much reduced in number and severity. Because there was a decided improvement maintained for a 12 to 14-month period, the results in these 3 patients were classified as fair. One of the patients was subsequently found to require further treatment with radioactive iodine because of return of function of the thyroid gland.

The results in 2 patients were classified as poor. These patients were both psychotic and difficult to evaluate.

Two patients who had severe angina during their paroxysms of tachycardia continued to experience occasional episodes of tachycardia after treatment with I^{131} but no longer suffered anginal pain with these attacks. Pain no longer occurred in association with the tachycardia although the ventricular rate

w s at least as rapid as it wes in the paroxy ns observed before treatment.

Discussion

The mechanism of action of radioactive i line in abating and reducing the number o attacks of paroxysmal tachycardia in e thyroid subjects is difficult to understand. C nsideration was given to the possibility that r lative hyperthyroidism might have been p esent in these patients, despite the absence o any clinical or laboratory evidence for t yroid hyperfunction. However, it is extremely improbable that all the patients in this series who obtained favorable results could have had masked hyperthyroidism.

The fundamental genesis of the exaggerated cardiovascular responses, manifested by tachycardia, increased pulse pressure, booming heart sounds, systolic murmurs, increased blood volume and decreased circulation time in hyperthyroidism is not fully understood.[1] No constant or specific myocardial lesions are found in the hearts of patients who have died of thyrotoxicosis.[1] In this condition, however, there is an apparent hypersensitivity to circulating epinephrine.[4] Furthermore, it has been shown by Raab[5] that the heart in hyperthyroidism contains more epinephrine than in the euthyroid state. It is well known that epinephrine increases the irritability of even the normal heart. It is possible, therefore, that at least some of the cardiovascular manifestations commonly observed in hyperthyroidism may be related to the effects of epinephrine. This would seem a plausible explanation for the frequent occurrence of such arrhythmias as atrial tachycardia and fibrillation in patients with hyperthyroidism. This hypothesis, however, cannot explain how the production of a hypothyroid state often abolishes these arrhythmias in euthyroid patients. It may, of course, be theorized that the epinephrine content of cardiac muscle in our series of euthyroid patients is more than normal, or that the heart in this condition is relatively sensitive to normal amounts of thyroid, but evidence to support such a theory is lacking. It is also possible that in euthyroid patients with arrhythmias the irritability of the cardiac muscle is such that it cannot tolerate normal levels of thyroid hormone.

Ullrick and Whitehorn[6] have demonstrated that under the influence of thyroid hormone the basic atrial metabolism is more markedly increased than that of the ventricle. The finding of an unusual sensitivity of the atrium to the action of thyroid hormone offers a physiologic basis for the atrial tachycardias that are so characteristic of hyperthyroid heart disease. By treatment of the euthyroid patient with radioiodine we probably decrease the level of atrial metabolism and thus the excitability. The change in atrial metabolism probably prevents recurrence of the tachycardias. Freedberg[7] stated "a significant number of euthyroid patients with persistent auricular fibrillation have demonstrated a reversal to normal sinus rhythm after the induction of hypothyroidism."

It is interesting that 2 of 3 patients who previously had precordial pain during the paroxysms, no longer had pain with recurrent attacks after treatment with radioactive iodine. It has been suggested that radioactive iodine, when administered for treatment of angina pectoris, lesseńs the work of the heart. However, in our 3 patients with recurrent paroxysms of tachycardia after I^{131} treatment, the heart rate was at least as fast as before treatment. Therefore, it seems doubtful that the work load of the heart was really reduced by the I^{131} during a pain-free episode of tachycardia. However, it is possible that in the hypothyroid state the metabolic requirements of the myocardium may be reduced. Thus, with lessened demand for coronary flow, myocardial ischemia and angina might be less likely to occur. This could account for the brilliant success of the treatment for angina pectoris by the induction of hypothyroidism.[3, 8]

Whatever may be the mechanism by which the reduction in thyroid function decreases the incidence of arrhythmias, it seems clear that the administration of I^{131} is a simple, convenient, and relatively safe method for producing hypothyroidism and preventing

supraventricular cardiac arrhythmias. The use of propylthiouracil for the same purpose was investigated by us in another group of euthyroid patients.[9] Although this drug was often found effective in reducing the frequency of paroxysms of arrhythmia through depression of the thyroid function, it was considered to be less practical and less safe than I^{131}.

Summary

Twenty-five euthyroid patients with paroxysmal supraventricular tachycardias were treated with radioactive iodine in an attempt to prevent recurrence of the paroxysmal arrhythmias. The production of a relative degree of hypothyroidism appears to be necessary in order to abolish episodes of supraventricular tachycardias in previously euthyroid patients resistant to other forms of treatment. The mechanism by which such attacks are prevented by suppressing thyroid function is not clear and should be studied further. Of the 25 euthyroid patients treated, 20 obtained good results. In 3 patients, the results were considered fair. In the remaining 2 patients, both of whom were psychotic, the treatment failed. In euthyroid individuals with paroxysmal supraventricular tachycardias that do not respond to the usual measures, radioactive iodine is often an effective agent for prevention of further attacks.

Addendum

Since this study was submitted for publication 8 additional cases of tachycardia were successfully treated with I^{131}.

Acknowledgment

We would like to thank Mr. and Mrs. Philip Raisin, Mr. and Mrs. E. D. Mitchell, Mr. and Mrs. F. Kaufman, and Mr. Beldon Katleman, whose financial assistance made this study possible.

Summario in Interlingua

Vinti-cinque patientes euthyroide con paroxysmal tachycardias supraventricular esseva tractate con iodo radioactive in un effortio de prevenir recurrentias del arrhythmia paroxysmal. Le production de un grado relative de hypothyroidismo pare esser necessari pro abolir episodios de tachycardia supraventricular in patientes previemente euthyroide qui se ha monstrate resistente a altere formas de tractamento. Le mechanismo per que le suppression del function thyroide resulta in le prevention de tal attaccos non es clar e merita studios additional. Le resultatos obtenite esseva bon in 20 del 25 patientes euthyroide tractate. In 3 patients le resultatos esseva considerate como "sufficiente." In le remanente 2 patientes—ambos psychotic—le tractamento falleva. In euthyroide individuos con tachycardia supraventricular paroxysmal non respondente al mesuras usual, iodo radioactive es frequentemente un agente efficace in le prevention de attaccos additional.

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Intramural Hemorrhage in Coronary Atherosclerosis

By THOMAS M. BLAKE, M.D., AND PHILIP K. SPRINGER, B.S.

The mechanism of the development of acute occlusion of the coronary arteries is subject to considerable discussion. Intramural hemorrhage has been suggested as a cause of acute occlusion by the hematomatous enlargement of atheromata without associated thrombosis. By a systematic study of coronary arteries with a special technic of injection and clearing of the vessels the frequency of this mechanism was determined.

ATHEROSCLEROSIS is present to some extent in almost every adult in the United States,[1-3] and occlusive lesions of coronary arteries are found frequently at autopsy in young people who die of noncardiac causes and in whom there had been no clinical evidence of heart disease.[2, 4] Atherosclerosis itself, then, is usually asymptomatic and is important chiefly as a basis for superimposed lesions that result in *acute* occlusion of arteries, especially coronary arteries. The mechanisms whereby an asymptomatic atheroma suddenly becomes the seat of such a catastrophic complication are not known. A review of the literature indicates that hemorrhage within the substance of an atheroma may well be at least one significant factor.[5-7] When looked for, such hemorrhages can usually be found in association with acute occlusions and Paterson, who is largely responsible for this observation, has suggested that they may serve to initiate thrombosis. Wartman[6] and Paterson[8] also have described occlusion of coronary arteries by hematomatous enlargement of atheromata without associated thrombosis.

The study reported here was undertaken to determine the incidence of intramural hemorrhage in the coronary arteries of the population at large by means of a technic that allows the stereoscopic study of large segments of arteries and facilitates the recognition of hemorrhages.

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This work was supported in part by grants from the Eli Lilly Research Laboratories, The Adams County Heart Society, and the Mississippi Heart Association.

MATERIAL AND METHOD

Hearts were obtained from every second autopsy done by each prosector in the Department of Pathology of the University Hospital. Only those from children under 5 years of age were excluded. The hearts were placed in normal saline solution at the time of autopsy and refrigerated at 1 to 2 C. for not more than 48 hours—usually 12 to 24 hours. At the time of study they were warmed to 37 C. and the coronary arteries washed with saline by a method described by Durlacher and co-workers[9] and used by Hamilton and Mowbray.[10] When the outflow from the coronary sinus was clear, the perfusion fluid was changed to a 1:8 suspension of Higgins' engrossing ink in water as suggested by Winternitz and associates[11] and the injection was continued until the myocardium was black. The intact heart was then fixed in 10 per cent formalin. Later the subepicardial portions of the coronary arteries were dissected and their adventitia was removed. The remaining parts of the vessels were cut into short segments, cleared by a modified Spalteholz method,[11] and mounted in clear plastic.[12] Tissue for routine microscopic study was taken from the coronary arteries before mounting, and the hearts were studied grossly and microscopically by the usual technics after the arteries had been removed.

The cleared, injected, unstained arteries were studied stereomicroscopically and hemorrhage was recognized by color or identifiable erythrocytes. No attempt was made to evaluate the observations quantitatively; only the presence or absence of intramural coronary arterial hemorrhage was recorded for each heart.

RESULTS

Table 1 shows that no intramural hemorrhage was found in the coronary arteries of any patient less than 45 years old. In men over this age the incidence was 70 per cent; in women, 28 per cent. The mean age of the 27 men in this group was 65 years and that of the 18 women 58. There were 14 men and

TABLE 1.—*Incidence of Intramural Hemorrhage in Coronary Arteries of Human Subjects Male Ages Ranged from 12 to 85, Female Ages from 13 to 87*

Age	White						Negro						Total					
	Males			Females			Males			Females			Males			Females		
	Pts.	Hem.	% Hem.	Pts.	Hem.	% Hem.	Pts.	Hem.	% Hem.	Pts.	Hem.	% Hem.	Pts.	Hem.	% Hem.	Pts.	Hem.	% Hem.
45 and over	16	11	69	7	2	29	11	8	73	11	3	27	27	19	70	18	5	28
Under 45	4	0	0	4	0	0	3	0	0	5	0	0	7	0	0	9	0	0
Total	20	11	55	11	2	18	14	8	57	16	3	19	34	19	56	27	5	19
Summary	31 whites with 13 hemorrhages = 42%						30 Negroes with 11 hemorrhages = 37%						61 patients in all with with 24 hemorrhages = 39%					

TABLE 2.—*Incidence of Intramural Hemorrhage as Related to Amount of Atherosclerosis*

Degree of atherosclerosis	Males			Females			Total		
	Pts.	Hem.	% Hem.	Pts.	Hem.	% Hem.	Pts.	Hem.	% Hem
None	6	0	0	4	0	0	10	0	0
Little	7	3	29	11	0	0	18	2	11
Moderate-to-marked	21	16	81	12	5	33	33	22	67
Total	34	19	56	27	5	19	61	24	39

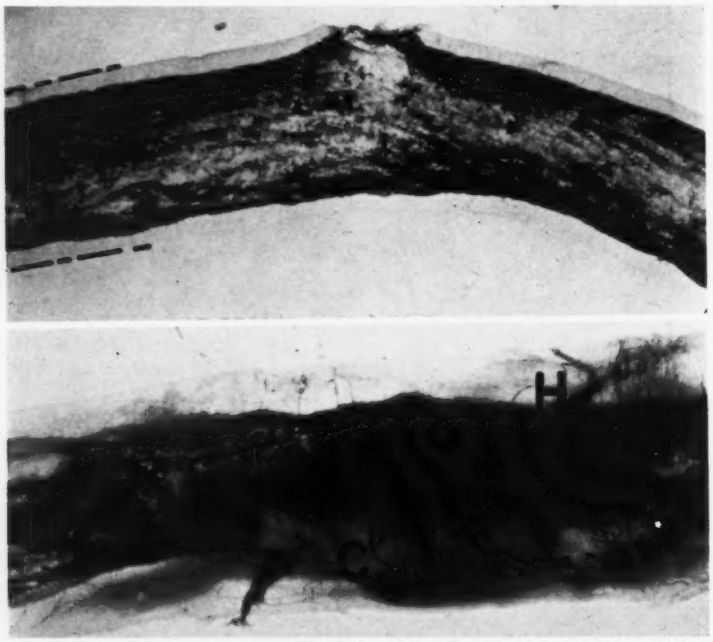

FIG. 1 *Top.* Normal coronary artery. The intima is outlined by ink particles which give it a "tree-bark" appearance. Note the smooth, translucent wall which is seen tangentially and is of uniform thickness. Its outer edge is indicated by inked lines. × 7.

FIG. 2 *Bottom.* Intramural hemorrhage and vasa vasorum. Note irregularity of thickened arterial wall. Some of the opacity in the center of the specimen is evidently calcium (*C*). × 7.

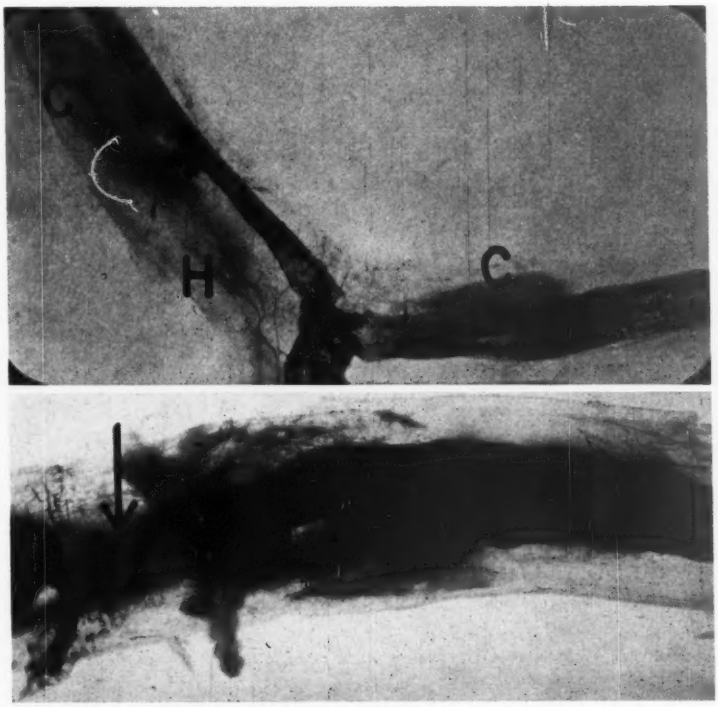

FIG. 3 *Top.* Intramural hemorrhage and vasa vasorum. Note the thick wall and, especially, the vasa vasorum ramifying in a small area of hemorrhage (*H*). The denser opacities probably represent calcium (*C*).

FIG. 4 *Bottom.* Intramural hemorrhage and vasa vasorum. The 3 small channels at the left of the specimen (arrow) apparently represent an old area of occlusion with recanalization. (The transverse artifact was made by a string used in labeling.) This patient died of an acute myocardial infarct. × 7.

5 women in the series who were 65 or older, and the incidence of intramural hemorrhage in these small groups was 80 and 60 per cent, respectively. There was no significant difference between the findings in Negroes and those in white subjects.

The degree of atherosclerotic involvement of the arteries in each case was noted arbitrarily as none, little, or moderate-to-marked on the basis of gross observation. Table 2 indicates that hemorrhage was clearly more common with more extensive disease.

There were 20 patients in the series who were defined as hypertensive on the basis of a recorded blood pressure of 150 or more systolic or 90 or more diastolic at some time during hospitalization. Ten of these (50 per cent) had intramural hemorrhage. Seven of the 12 men in this group (58 per cent) and 3 of the 8 women (38 per cent) showed intramural hemorrhage. Only 1 of the hypertensive subjects was less than 45 years old and no hemorrhage was found in his arteries. If he is not counted, the incidence of intramural hemorrhage in the hypertensive group, all 45 or over, was 53 per cent. In the 25 patients 45 or older with normal blood pressure the incidence was 56 per cent. Thus there was no correlation between intramural hemorrhage and blood pressure.

Recent myocardial infarcts were found in 6 hearts, 5 men and 1 woman, and intramural hemorrhage was present in only 4 of these—all men. Both of the patients with myocar-

dial infarction without hemorrhage were hypertensive Negroes, a 42-year-old man and a 47-year-old woman, and infarction had not been suspected clinically in either case. Each had congestive heart failure and died in uremia. Only 4 patients were receiving anticoagulant therapy at the time of death. Three of these were being treated for myocardial infarction and 1 for angina, and in none was the prothrombin concentration significantly depressed.

Vasa vasorum were demonstrated in many atheromata. These arose from the lumen of the artery in some instances and came from the outer parts of the wall in others. Many atheromata contained no injected vasa vasorum and often none was seen in the vicinity of frank hemorrhage.

Discussion

Atherosclerosis is nearly ubiquitous in man—at least in Americans and Europeans—and not infrequently even produces complete occlusion of coronary arteries without clinical evidence of heart disease. It is the *acute* occlusive lesions of arteries that sometimes develop in association with atheromata that constitute the real threat posed by atherosclerosis, and these must be considered complications of the disease rather than an inevitable consequence of it. While it is obvious that ultimate hope lies in the prevention of atherogenesis or resolution of lesions already present, it seems worthwhile until this goal is reached to determine if possible the factors responsible for these complications. Intramural hemorrhage has been suggested as a factor and the data reported here emphasize the frequency with which hemorrhage is found as a part of atherosclerosis. It should be pointed out that the method described demonstrated only fresh hemorrhages. If some method of recognizing old ones like that described by Paterson and associates[13] had been used, it is likely that many more would have been found.

It is interesting that the frequency of these lesions was no greater in the presence of hypertension than with normal blood pressure. One very pertinent question, the effect of anticoagulant drugs on the incidence of intramural hemorrhage, remains completely unanswered, since no patient in our series had significantly depressed prothrombin activity at the time of death.

Our observations with regard to vascularization of the lesions are not conclusive but are in accord with those of Paterson and Winternitz and demonstrate that atheromata, like other tumors, have a blood supply. Whether the hemorrhages that occur in their depths are passive as a result of simple necrosis due to "outstripping" of the blood supply, infarction of the atheroma as the result of occlusion of the nutritive vasa, or active rupture of the vasa vasorum, remains speculative. The stereoscopic method used, however, makes it clear that most of the hemorrhages are deep in the wall of the vessel without any communication with the lumen.

The possibility that these hemorrhages are of clinical significance in the production of occlusive complications of atherosclerosis remains an interesting hypothesis. Their existence, however, is a fact and suggests that coronary arteries should be regarded as complicated organs dependent on their blood supply, like the heart itself. It is possible that study of this microscopic blood supply and its disorders may yield information of importance in the control of heart disease.

Conclusions

Intramural hemorrhage is a common complication of atherosclerosis and was found in 70 per cent of men and 28 per cent of women over 45, but in no patient under that age. The possibility that these hemorrhages may be a factor in the precipitation of acute occlusive lesions of coronary arteries is discussed.

Acknowledgment

The authors wish to express their appreciation to the staff of the Department of Pathology of the University Hospital for their cooperation in providing the autopsy material. The technical assistance of Mr. Lacy P. Fraiser and Mr. Richard L. Blount is gratefully acknowledged.

SUMMARIO IN INTERLINGUA

Hemorrhagia intramural es un complica-
n commun de atherosclerosis. Illo esseva
ontrate in 70 pro cento del masculos e 28
o cento del femininas de etates de plus que
annos sed in nulle patiente de un etate
us juvene. Es discutite le possibilitate que
e hemorrhagia es un factor in le precipita-
n de acute lesiones occlusive in le arterias
ronari.

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Clark, W. S., Kulka, P., and Bauer, W.: Rheumatoid Aortitis with Aortic Regurgitation. An Unusual Manifestation of Rheumatoid Arthritis (Including Spondylitis). Am. J. Med. **22**: 580 (April), 1957.

Aortic regurgitation and rheumatoid arthritis have been observed concurrently in 22 male patients between 18 and 64 years of age all but 2 of whom had spondylitis. Fifty-nine per cent of the patients had uveitis. The cardiac lesions tended to be strikingly similar to those of syphilitic heart disease with aortic regurgitation. However, the destructive lesions of the aortic wall remain circumscribed and do not extend beyond the ascending portion of the artery. The cardio-aortitis is thought to represent a systemic manifestation of rheumatoid disease because of the temporal relation between onset of cardiac signs and activity of the arthritis, the absence of evidence implicating syphilis or rheumatic fever, and the basic resemblance of the microscopic changes in the aorta and heart to those of other rheumatoid lesions.

KURLAND

Total Electrical Alternation in Pericardial Disease

By David Littmann, M.D., and David H. Spodick, M.D.

Simultaneous electrical alternation of atrial and ventricular components can occur in malignant and sometimes tuberculous pericardial disease and is due, apparently, to a rotary pendular movement of the heart at a rate that differs from the pulse. This oscillation occurs only during effusion with tamponade and clears with paracentesis. It is thought to be the result of unusual freedom or release from the normal pulmonary and thoracic restraints.

SEVERAL years ago one of us observed a curious coincidence of phenomena in a patient very ill with tuberculous pericarditis. In addition to the findings of pericardial effusion there was an alternating pulse and an alternating friction rub. The electrocardiogram obtained at the same time exhibited extensive electrical alternation of the QRS and T waves, and, though it was not appreciated at the time, alternation of the P waves. Unfortunately, except for the electrocardiogram, none of the other phenomena was graphically recorded and all disappeared not long after the effusion was tapped. Antibiotic therapy was instituted and the pericarditis cleared completely. None of the alternating phenomena ever reappeared.

Not long thereafter another case of electrical alternation was observed in a patient with malignant hemopericardium. Here too, simultaneous P wave alternation, though present, was initially overlooked.

In June 1955, McGregor and Baskind[1] reported 3 cases of simultaneous alternation of atrial and ventricular complexes resulting from pericardial effusion and offered an explanation for the phenomenon. In the 2 years since this review 2 more examples of electrical alternation of atria and ventricles were seen and recognized at the Veterans Administration Hospital in West Roxbury. Both were the result of malignant pericardial disease with tamponade. Both patients were profoundly ill and studies were necessarily limited. However, careful removal of small quantities of pericardial contents, (60 ml. in one patient and 150 ml. in the other resulted in abolition of the alternating phenomena. These 4 cases are offered as a relatively large addition to a meager literature on the subject.

From the Veterans Administration Hospital, West Roxbury, Mass.

Material

Case 1. A 30-year-old man was admitted to the hospital complaining of pleuritic pain for 1 week and cough, night sweats, and weight loss for the preceding 3 weeks.

Examination revealed an acutely ill man with a temperature of 100.4 F., a blood pressure of 102/85, and a pulse of 124. There were dullness and altered breath sounds over the right base. The heart was enlarged, the sounds were distant, and a friction rub was heard with every other beat. Pulsus alternans was present. The electrocardiogram disclosed extensive ventricular and limited atrial alternation (fig. 1).

X-rays showed pericardial and right pleural effusions together with areas of pneumonitis. Tubercle bacilli were recovered from the sputum and eventually from the pericardial and pleural effusions.

Pericardiocentesis was performed shortly after admission and 300 ml. of straw-colored fluid were obtained. This served to abolish the manifestations of tamponade and the alternating phenomena. Antibiotic therapy was also instituted. The fever and other constitutional symptoms receded by the sixth day and improvement was continuous thereafter.

Case 2. A 53-year-old truck driver was admitted to the hospital with epigastric pain, weakness, chills, and malaise. There was a history of cough for 5 years and increasing dyspnea for 1 year.

Physical examination disclosed an acutely ill and dyspneic man with a blood pressure of 138/84, a temperature of 97.6 F., and a pulse of 108. The heart sounds were distant and a systolic murmur was noted. A 40-mm. Hg drop in systolic blood pressure occurred during inspiration.

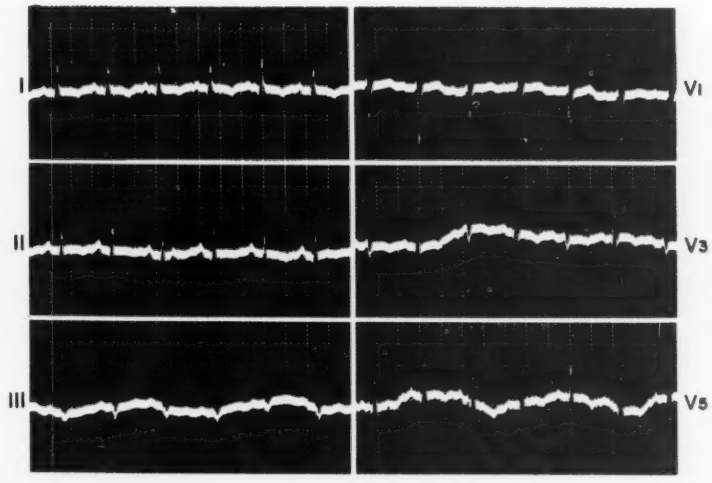

FIG. 1. Case 1. Tuberculous pericarditis with tamponade. P alternation is best seen in V_5, T alternation in I and II.

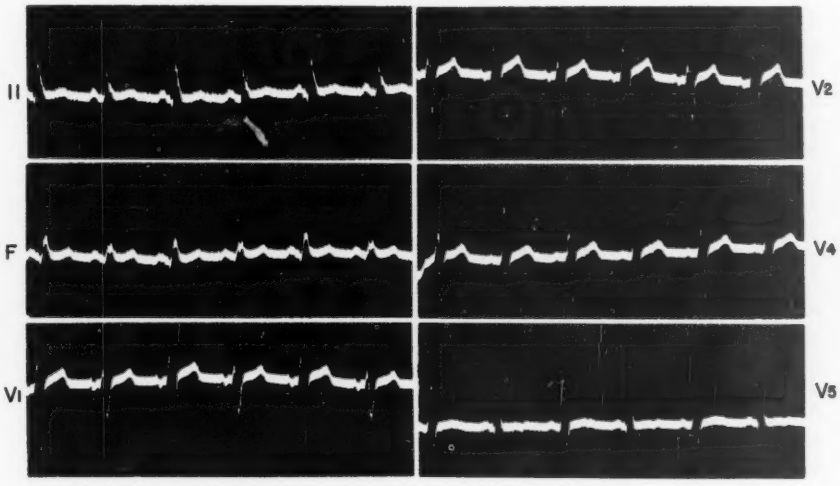

FIG. 2. Case 2. Malignant hemopericardium with tamponade. P alternation is best seen in F(aV_F) and V_1, T alternation in V_5.

X-rays showed an enlarged heart shadow and p lmonary congestion; a subsequent electrocardio- gram demonstrated total electrical alternation (fig. 2 . On the third hospital day the venous pres- s re was 370 mm. of water and the circulation t ne, arm-to-tongue, was 37 seconds. On the fol- l ving day, because of leg tenderness, heparin was a ministered. However, he became cyanotic and t hypneic, his blood pressure could not be ob- t ned, and he died on the fifth hospital day.

At autopsy the pericardium contained 1,300 ml. of dark liquid blood. There was granulomatous involvement of the parietal pericardium secondary to adenocarcinoma of the right lung. There were 5 pinhead-sized metastases on the visceral pericardium.

Case 3. A 30-year-old man in the latter stages of Hodgkin's disease was transferred to the West Roxbury Veterans Administration Hospital for terminal care. The major complaints included

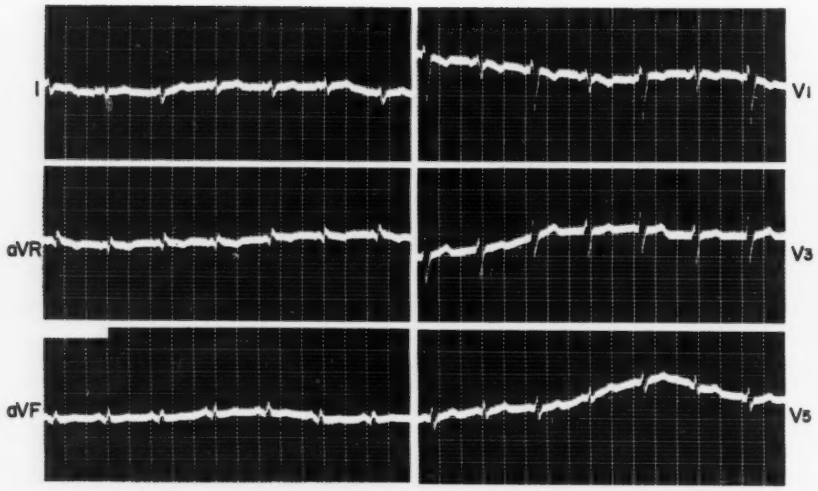

FIG. 3. Case 3. Hodgkin's disease with pericardial involvement and tamponade. Alternation of all components is best seen in V_1.

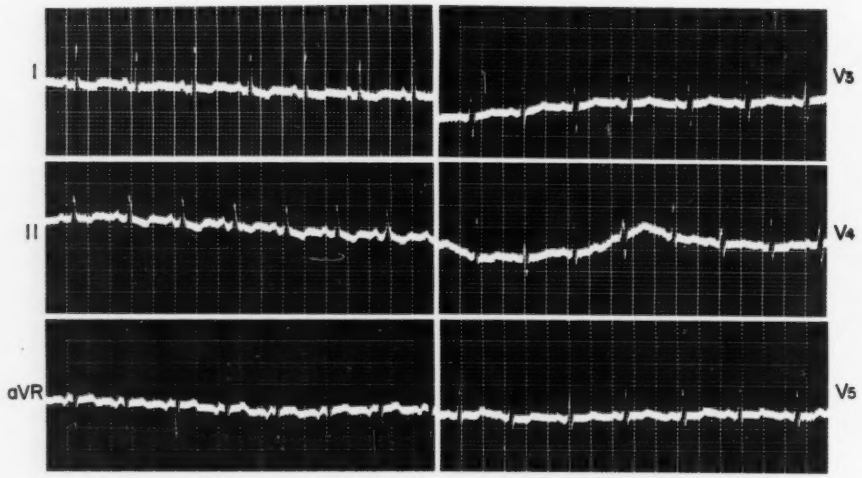

FIG. 4. Case 4. Malignant hemopericardium with tamponade. Alternation of all components is best seen in V_4 though changes in P waves are minimal and poorly noted. They are less well seen in lead I.

dyspnea, chest pain, and cyanosis. The blood pressure was 100/82 and the pulse was 124. A 15-mm. paradoxical variation in blood pressure was noted. The heart sounds were distant and an apical systolic murmur was heard with every other beat. The roentgenogram revealed pericardial and left pleural effusions. The electrocardiogram showed simultaneous atrial and ventricular alternation (fig. 3), which disappeared following paracentesis of 150 ml. of yellow fluid.

Despite all therapeutic efforts the patient died on the thirty-seventh hospital day. Postmortem examination showed widespread Hodgkin's disease with involvement of the pericardium and with focal myocardial lesions. The pericardium contained 1,000 ml. of clear yellow fluid.

Case 4. A 43-year-old man with a 1 month history of rapidly progressive dyspnea, fatigue and chest pain was admitted to another hospital where a diagnosis of pericardial effusion was made

P acentesis yielded bloody fluid which was shown t contain malignant cells.

The patient arrived at the West Roxbury Vete ns Hospital with evidence of pericardial effus n and tamponade, a temperature of 100.6 F. and a eart rate of 120. The area of cardiac dullness w s increased, the heart sounds were distant and a aradoxical pulse was noted. The electrocardiog m showed the presence of total alternation (g. 4). Paracentesis was performed shortly after a mission and 350 ml. of bloody fluid were re- n ved. The initial pressure of 280 mm. of water w s reduced to 220. At the conclusion of this pro- c lure both the paradoxical pulse and the elect cal alternans disappeared.

Within a few hours rapid recurrence of tampo- n de made another tap necessary and a polyethy- l ne catheter was left in the pericardium. A total o 1,100 ml. of grossly bloody fluid was removed d ring the next 24 hours. A biopsy of a supra- cl vicular node disclosed epidermoid carcinoma, probably pulmonary in origin. Eventually peri- cardial bleeding stopped and following a course o radiotherapy the patient was returned to the original hospital.

Discussion

Electrical alternation can, as a matter of definition, involve any component of the electrocardiogram. There may be changing individual wave forms, changing intervals, or combinations of the two. By common agreement, however, the term "electrical alternation" is reserved for records having a constant interval between alternating complexes, a constant site of origin (identity of pacemaker), and demonstrated independence from respiratory activity. The last is important in cases where the heart rate could be just twice the respiratory frequency.

Isolated alternation of the P waves is extraordinarily rare. It has been reported on nly 2 occasions; once, apparently, as the r sult of drug intoxication[2] and in another p tient with primary amyloidosis of the h art.[3] Alternation limited to the ventricular c mplex is also unusual. For example, Ham- l rger, Katz, and Saphir[2] encountered only instance in 10,000 consecutive records. Feld- an[4] found none in 6,000 tracings while alter and Schwartz[5] collected 5 cases in 059 patients. It is clear, however, that inor degrees of alternation could be obscured by other electrocardiographic variations.[2]

Simultaneous alternation of all electrical components has been reported 10 times. In addition to the 3 cases of their own McGregor and Baskind[1] collected 6 others from the literature of which only 2 had been detected by the reporting investigators. One additional case is noted from an electrocardiogram in Wood's textbook[6] illustrating electrical alternans of the ventricular complexes. It was obtained from a patient with malignant hemopericardium and demonstrates well-marked P wave alternation best shown in lead III.

The first case of total electrical alternation recognized as a consequence of pericardial effusion was reported by McGregor[7] in 1946. However, 4 years earlier, Reisinger, Pekin, and Blumenthal[8] published a similar record from a patient with malignant hemopericardium. Also, in 1945, Fletcher[9] in reporting another patient with neoplastic pericardial effusion noted QRS alternation while overlooking similar changes of the P waves.

Electrical alternation of the ventricular components is classically attributed to coronary heart disease or myocarditis. Simultaneous alternation of atrial and ventricular complexes might, therefore, result from myocardial disease of all chambers. However, this has not been demonstrated at postmortem examinations of patients who during life exhibited this phenomenon. It is, apparently, encountered only in the presence of serious pericardial disorders with tamponade.

Careful inspection of the records exhibiting simultaneous atrial and ventricular alternation suggests that the alternating pattern is a manifestation of varying axis and that this in turn is due to an actual change of cardiac position occurring with every other beat. It is commonly best seen in the midprecordial leads, with the complexes resembling first the waves from an adjacent lead to one side, possibly to the right of the selected position, then resembling those to the left, and alternating between the 2 even during suspended respiration. The variation does, in fact, except for

the frequency, simulate that noted as a consequence of deep respiration. Where it is large enough to be well seen in the limb leads, the axis shift of the P waves is in the same direction as the QRS complexes. This alternation of pattern involving all electrocardiographic components obtained during held respiration is entirely consistent with an alternating cardiac position and is not well explained in any other way. The coincidental mechanical alternations (friction rubs, murmurs, pulsus alternans) do not detract from this hypothesis. The gross variations of cardiac position suggested by the electrocardiograms would be of sufficient degree to distort the great vessels and interfere with cardiac filling or emptying. It would also be sufficient to result in changing intensity of coincidental friction rubs or murmurs.

The reason for anatomic alternation of cardiac position was first proposed by McGregor and Baskind,[1] who suggested that "The heart suspended in a large sac of fluid should move more than the normal organ." The helical arrangement of the great vessels together with the spiral musculature of the heart cause a normal systolic rotation of the heart about its long axis. The lungs and mediastinal structures, however, exert a gentle restraining influence that helps to return the heart to its diastolic position. In the presence of a sufficiently large effusion, these restoring forces are separated and insulated from the heart, and the normal cardiac rotation is not completely halted and reversed at the end of systole. The succeeding beat can then add its movement to a still partially rotated heart. In this manner, by the summation of rhythmic pushes, a periodic rotary oscillation can be established somewhat like the rotating pendulums of some clocks. The natural frequency of this cardiac oscillation varies somewhat with the heart size, position, and build of the patient. It would probably be different, however, from the cardiac rate so that the normal cardiac movement would be expected at some times to enhance the degree of pendular rotation and at other times to oppose it. This can result in a variety of rhythmic positional changes.[1, 11] The one most easily recognized however, and the least likely to be confused with respiratory variations is the change of position that occurs with every other beat and that causes electrical alternation of both atria and ventricles. It is of some interest that this phenomenon occurs almost invariably in the presence of tachycardia. Three of the 4 cases presented here had pulse rates of 120 to 12 while the fourth had a rate of 100 per minute. The cases reported elsewhere had similar frequencies. It would appear, therefore, that the natural oscillatory rate of the heart would fall between 50 and 65 per minute.

The largest and most clearly inscribed wave forms are contained within the QRS complex and it is here that electrical alternation is most obvious. The T waves are always secondarily involved but, because they are lower and more diffuse, T-wave alternation is less well seen. The P waves are normally the smallest deflections, and alternating changes in these complexes are slight and easily overlooked unless they are especially searched for or are unusually prominent.

One important observation regarding total electrical alternation remains unexplained by the relatively simple hypothesis of varying cardiac position. It is seen, apparently, only in serious pericardial involvement, either tuberculous pericarditis or malignant disease.[10] It is present only during tamponade and clears with paracentesis. This implies an added factor of interference with cardiac filling, a detail that may play a critical but presently unknown part. One element that may contribute to this phenomenon is the relatively greater thickness and stiffness of the parietal pericardium in tuberculous infection and in malignant disease than in benign pericarditis. It appears likely that despite the presence of effusion considerable restraint upon abnormally free cardiac movement is still exerted by the lungs and other thoracic structures through a relatively normal and yielding parietal pericardium. However, this would be less effective or even nonexistent through a taut, thick, or stiff covering. This is the situation that permits exaggerated free-

do n of movement and the resultant electrical al rnation. A reduction in pericardial conte s leads to a lessening in tenseness and stiffne s of the parietal membrane and once more pe mits transmission of the limiting and rest ring forces. We have not, in recent years, se n severe tamponade in relatively benign pe icardial disease. It is considered likely, ho vever, that alternation could occur with la ge effusions of any type when accompanied b high intrapericardial pressures.

Curiously, electrical alternation may wane an l disappear despite continuing tamponad e.[1, 7, 8] Possibly concomitant changes in fl id viscosity, the development of adhesions, or increasing feebleness of cardiac pulsation may interfere with the maintenance of rotational moment.

Summary

Simultaneous electrical alternation of atrial and ventricular components is uniquely related to serious pericardial disease with effusion and tamponade.

Present theories for the genesis of this phenomenon are reviewed and amplified. In the presence of a suitable effusion it is hypothecated that a rotary pendular movement of the heart can occur as the result of an unusual degree of freedom from the normal mediastinal and pulmonary restraints. When this oscillation bears a 1:2 relationship to the heart rate, an alternating difference in cardiac position becomes manifest in total electrical alternation.

Four patients who exhibited synchronous electrical alternation of atria and ventricles are presented and discussed.

Summario in Interlingua

Le simultanee alternation electric de componentes atrial e ventricular es unicamente relationate a serie morbo pericardial con effusion e temponage.

Le theorias currente relative al genese de iste phenomeno es passate in revista e amplificate. In le presentia de un appropriate effusion, le hypothese es postulate que un movimento pendular rotatori del corde pote occurrer como resultato de un grado inusual de libertate ab le normal restrictiones mediastinal e pulmonar. Quando iste oscillation es relationate al frequentia cardiac in un relation de 1:2, un differentia alternante in le position cardiac se manifesta in total alternation electric.

Es presentate e discutite le casos de 4 patientes qui exhibiva un synchrome alternation electric del atrios e ventriculos.

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Effectiveness of an Oral, Nonmercurial Diuretic:
Clinical Trial with Thirty-Five Patients

By BENJAMIN WAINFELD, M.D., JACOB J. YARVIS, M.D., AND I. RICHARD SCHWARTZ, M.D.

In a previous trial of aminometramid on 30 patients with peripheral edema, 19 became refractory to the drug. These 19 patients and another group of 16 with peripheral edema or ascites were placed on another nonmercurial diuretic aminoisometradine, which had shown promise in previous studies in animals and man. This group of 35 patients who had previously required frequent injections of mercurial diuretics were treated with the new diuretic for at least 8 months. Conclusions of this study are presented.

IN A previous report,[1] dealing with the clinical evaluation of aminometramid (Mictine) in a group of 30 patients with peripheral edema due to congestive heart failure, 19 patients who had responded well at the outset developed resistance to the action of the drug after 5 to 20 weeks of therapy. These 19 patients were then given another nonmercurial diuretic drug, a derivative of pyrimidinedione, known as aminoisometradine (Rolicton).* The initial response of this group of 19 patients to the new drug appeared promising and another study was organized to include these patients plus a new group of patients with congestive heart failure. Five patients with ascites and edema caused by Laennec's cirrhosis were also added to the study.

Impetus was given to our efforts to find a satisfactory nonmercurial diuretic by the presence of over 150 patients weekly at the diuretic injection clinic at this hospital. Problems associated with long-term therapy involving mercurial diuretics are well known and have been amply discussed in the literature.[2-9] It was therefore believed that a satisfactory nonmercurial drug would be of great value in the management of patients in whom the use of organomercurials was deemed inadvisable for one reason or another.[1]

From the Medical Clinic, Out-Patient Department, Kings County Hospital Center, Brooklyn, N. Y.

*The supply of Rolicton was kindly given by Dr. J. William Crosson, Assistant Director, Clinical Research, G. D. Searle & Co., Inc., Chicago, Ill.

MATERIALS AND METHODS

The group of 19 patients who had been receiving Mictine together with the new group of 16 patients were evaluated anew. They were all patients who had required weekly or biweekly injections for at least 6 months. They were screened for a 4-week period. All nonmercurial diuretic therapy was withheld, they were examined and weighed biweekly, and mercurial diuretic agents were administered as indicated by their clinical state. In this manner their individual requirements for medication were established. The group consisted of 35 patients who attended clinic regularly and participated in the study for at least 8 months. A few additional patients entered and left the study during this time but are not included because of insufficient observation. The criteria used in determining diuretic requirements were signs of weight gain, peripheral edema, pulmonary congestion, hepatic enlargement, and subjective symptoms of dyspnea and orthopnea. These also served as standards in evaluating success or failure of therapy. The age, diagnosis, and other pertinent data are given in table 1.

Each patient had a 6-foot roentgen film of the chest and a 12-lead electrocardiogram. In addition, levels of serum sodium, potassium, chlorides, and blood urea nitrogen were determined. These were used as a baseline in determining the biochemical effects of the diuretic agent under study. The examinations listed above were repeated periodically and the patients were observed initially and at last biweekly thereafter. At each visit special attention was paid to weight gain or loss and to the existence of peripheral edema. Heart and lungs were examined routinely and any dyspnea, orthopnea, or symptoms of toxicity were noted.

They were then given Rolicton, which was obtainable only at each clinic visit. The dosage varied from 400 mg. to 5 Gm. daily and was changed as the patient's clinical condition required.

TABLE 1.—*Clinical Data on Thirty-Five Patients*

ient no., ge, sex	Diagnosis	Number of injections per week	Dose Rolicton (Gm.)	Result
51, M	ASHD, Laennec's cirrhosis	1	1.2	Good, injections spaced out 10-14 days
53, F	RHD, Hyperthyroidism	2	5.0	Poor
42, M	RHD	1	1.6	Good, injections spaced out 10-14 days
41, M	ASHD	1	0.8	Excellent, no further injections
61, F	ASHD	1	0.8	Good, injections spaced out 10-12 days
47, M	RHD	1	1.0	Excellent, no further injections
71, M	ASHD	1	1.2	Good, injections spaced out 10-14 days
51, M	RHD	2	5.0	Poor
68, M	Cor Pulmonale, chronic pulmonary disease	2	2.0	Good, injections spaced out 6-10 days
67, M	ASHD, Diabetes mellitus	1	1.6	Good, injections spaced out 10-14 days
53, M	ASHD	1	1.2	Excellent, no further injections
61, M	ASHD	1	1.2	Excellent, no further injections
42, M	RHD	2	5.0	Fair, injections spaced out 7-10 days
48, M	ASHD	1	1.2	Very good, injections spaced 18-21 days
69, M	ASHD, HHD	1	1.6	Good, injections spaced out 10-14 days
63, M	ASHD	1	1.2	Excellent, no further injections
66, M	HHD	1	1.6	Excellent, no further injections
74, M	ASHD	1	1.2	Excellent, no further injections
67, F	ASHD	1	0.8	Excellent, no further injections
68, M	ASHD	1	0.8	Excellent, no further injections
57, F	HHD	1	1.2	Excellent, no further injections
63, M	ASHD	2	1.6	Good, injections spaced out 10-12 days
58, F	ASHD	2	5.0	Poor
74, M	ASHD	1	1.2	Good, injections spaced out 10-14 days
44, F	RHD	1	1.2	Good, injections spaced out 10-14 days
55, M	HHD	1	0.8	Excellent, no further injections
62, F	ASHD	2	5.0	Poor
53, F	RHD	2	5.0	Poor
61, F	ASHD	1	0.8	Excellent, no further injections
49, M	ASHD	1	1.0	Good, injections spaced out 14 days
42, M	Laennec's cirrhosis	2	5.0	Poor
58, M	Laennec's cirrhosis	2	5.0	Poor
64, F	Laennec's cirrhosis	2	5.0	Poor
56, M	Laennec's cirrhosis	2	5.0	Slight reduction in ascites and edema
61, M	Laennec's cirrhosis	2	2.0	Moderate reduction in ascites and edema

RHD—rheumatic heart disease; ASHD—Arteriosclerotic heart disease; HHD—hypertensive heart disease

RESULTS AND CONCLUSIONS

Two patients who had not responded to Mictine, cases 2 and 8, and who required biweekly mercurial injections did not respond to Rolicton either. The daily dose was increased to 5 Gm. in each case with no result; even at the maximum dose, no sign or symptom of toxicity was elicited. The patients continued to require mercurial injections as before. Of the remaining 17 patients who were transferred from Mictine to Rolicton, 9 responded well from the outset. They were maintained free of edema, with no further mercurial injections required for periods up to 32 weeks. The remaining 8 patients appeared to respond for periods ranging from 2 to 8 weeks, but then began to require mercurial injections again. However, whereas they had required weekly injections, these were now spaced out over 10 to 14 day periods. In 1 case, case 14, injections are now required about once in 18 to 21 days.

Of the 11 patients who previously had not received any oral drug, those responded best who had required injections once weekly or less frequently. Four patients no longer re-

quired injections at all, another 4 had their injections spaced out over longer periods of time. Three patients in severe congestive heart failure and requiring injections biweekly responded poorly. The patients who responded well are free of edema, show no sign of weight gain, and subjectively feel as well as they did with mercurial agents.

The patients with Laennec's cirrhosis showed only moderate response to the drug. Only 2 of the 5 patients studied showed any loss in weight and in ascites and peripheral edema. The remaining 3 gave no sign of improvement in their state.

Repeated biochemical studies revealed no significant changes from the baseline levels established at the start of the study and there were no symptoms of toxicity reported. The drug was uniformly well tolerated. It was found that if a total daily dose of 2 Gm. was insufficient to control fluid retention, little was gained by further increase in dose. Doses as high as 5 Gm. daily were well tolerated.

Inasmuch as patients with severe congestive failure requiring frequent mercurial injections were not benefited to any degree, it appears premature to conclude that a satisfactory nonmercurial oral diuretic has been obtained. The problem of fluid retention is still with us and continued search for an oral diuretic effective in advanced failure is warranted.

The optimum dose varied with each patient. It was found that 800 mg. to 1.6 Gm., 2 to 4 tablets in divided doses daily, were usually satisfactory. There was no special need to take the drug with meals.

Summary

Thirty-five patients with fluid retention caused by heart disease and Laennec's cirrhosis were studied in a clinical evaluation of Rolicton. Thirteen showed an excellent response to the drug, remaining comfortable clinically with no fluid retention at the end of 32 weeks of therapy. Eleven patients continue to require mercurial injections but these have been spaced out over longer periods of time. One patient requiring weekly injections is now controlled by 1 injection every 18 to 21 days. Five patients with severe congestive failure requiring 2 injections weekly were not benefited to any degree. Of 5 patients with Laennec's cirrhosis, 2 responded to treatment with a reduction in ascites and edema while 3 showed no response. No signs of biochemical abnormalities were demonstrated after repeated laboratory studies, and toxicity to the drug was not present in any patient. The optimum dose must be individualized for each patient but was found to lie between 800 mg. and 1.6 Gm. daily in divided doses. The drug appears to warrant a trial in cases of mild to moderately severe fluid retention due to congestive heart failure. It is of limited value in cases of severe congestive heart failure with extreme fluid retention. In all cases where mercurial therapy is contraindicated, clinical trial of the drug appears warranted.

Summario in Interlingua

Trenta-cinque patientes con retention de fluido causate per morbo cardiac e cirrhosis de Laennec esseva studiate in un evalutation clinic de Rolicton. Dece-tres monstrava un excellente responsa al droga. Illes se manteneva in un stato de comfortabilitate clinic sin retention de fluido al fin de un curso therapeutic de 32 septimanas. Dece-un patientes continua requirer injectiones de mercurial, sed iste injectiones es separate per plus longe intervallos. Un patiente qui requireva injectiones septimanal es nunc mantenite per un injection omne 18 a 21 dies. Cinque patientes con sever disfallimento congestive, qui requireva 2 injectiones per septimana, non beneficiava a grados significative. Ex le 5 patientes con cirrhosis de Laennec, 2 respondeva per un reduction del ascites e del edema, durante que le 3 alteres monstrava nulle responsa. Nulle signos de anormalitate biochimic esseva demonstrate per repetite studios laboratorial, e toxicitate como effecto del droga non esseva constatate in ulle del patientes. Le dosage optimal debe esser determinate pro omne patiente individual, sed il

e seva trovate que illo es inter 800 mg e 1,6 g
r die in doses dividite. Il pare que le droga
rita esser essayate in casos de leve o moder-
e retention de fluido attribuibile a conges-
re disfallimento cardiac. Illo es de pauc
lor in casos de sever disfallimento cardiac
ngestive con extreme grados de retention
fluido. In omne casos in que un therapia
ercurial es contraindicate, le essayo clinic
l droga pare esser justificate.

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In 3 sets of experiments in rabbits, an attempt was made to induce arteriosclerotic changes in pulmonary vessels. It was postulated that repeated emboli caused arteriosclerotic changes, not through organization of emboli, but through repeated arteriospasm and resultant changes in the nutrition of cells in the walls of the vessels because the blood supply was diminished. The experiments were, therefore, designed to induce spasm in the pulmonary vessels. To insure organization, repeated pulmonary air emboli were induced in 1 group of rabbits. Repeated air emboli induced changes compatible with arteriosclerosis in the pulmonary vessels. Arteriospasm was observed in the control animals at the time air emboli were induced. To cause spasm of vessels without emboli, adenosine-triphosphate was injected into another group of rabbits, and although spasm occurred, no arteriosclerotic changes were induced. In a third group of animals, the left pulmonary artery was ligated and emboli were induced in the right lung to see if any hormonal or reflex changes in the left lung resulted, which could cause arteriosclerotic changes. There was no evidence that any arteriosclerotic changes were induced by reflex or hormonal action.

Harvey

Reliability of Subjective Circulation Time Determinations

A Comparison Between Objective and Subjective Methods

By MURRAY M. MAHL, M.D., AND KURT LANGE, M.D.

When the fully objective dermofluorographic method of measurement of circulation time was compared with the subjective Decholin and saccharin methods, it was found that the values obtained with the subjective methods were often unreliable. The error was unpredictable in magnitude and occurrence, and was maximal in patients with failure.

THERE can be no doubt that the determination of the circulation time is one of the basic methods for the evaluation of circulatory efficiency. It is therefore highly important that the technics used be as accurate as possible. Therefore, the fully objective method of the dermofluorographic determination of circulation time was compared with the more generally used subjective methods.

To perform circulation time determinations properly for a complete circuit, 5 conditions must be fulfilled:[1] 1. The circuit must contain all essential parts of the circulatory apparatus, that is, a vein, the pulmonary circulation, an artery, arteriole, and capillary. 2. The circuit must be at basal conditions for the given individual; it must not have arterioles and capillaries abnormally dilated or contracted by purely local factors. 3. The point of observation or detection should permit the recognition of the arrival of the test substance in the capillaries and not in the arterioles or arteries. 4. The quantity of material injected must be large enough to be detected at the point of observation, even when mixed with an unusually large amount of blood, e.g., the blood volume of a heart in failure, with large residual blood volume. 5. The injected material should not influence the velocity of blood flow.

Most of the available methods of measuring circulation time are subjective, and thereby carry a certain intrinsic fraction o unreliability, as the reaction times of th patient and of the physician are involved i the perception of the signal or endpoint. Th subjective methods are responsible for man of the dubious results obtained, may var even in the same individual under differen conditions,[2] and are associated with a larg percentage of "blanks," i.e., the subjectiv response fails to appear.[3] In addition, they are often dangerous[4–7] and often cannot be performed in those cases where the determination of the circulation has decisive value, namely, in patients with enlarged hearts, in unconscious patients, and in small children with or without congenital heart diseases.

The previously available objective measurements of circulation time, such as the use of dye dilution studies[8] and radioactive substances, required complicated apparatus and considerable laboratory facilities.[7–10] In addition, they were not completely objective, not free of danger,[10–14] and not repeatable at short intervals.

The dermofluorographic circulation time is a completely objective automatic method of recording circulation time with fluorescein. The dermofluorograph[15] basically consists of a small compact search unit, containing a phototube rigidly aligned to a long-wave ultraviolet light source; the phototube is sensitive only to the green light emitted by fluorescein when excited by long-wave ultraviolet light. The output of the phototube is electronically amplified and recorded on a strip chart recording galvanometer. For the purposes of this study, the search unit was placed

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o the skin of the cheek. The instrument is p rtable, and the test is performed at the b dside. The time elapsing from the intra- v nous injection of 3 ml. of 5 per cent fluo- r scein solution to its arrival in the skin of t e face is recorded completely automatically. The method is repeatable and its accuracy l s within ±5 per cent. Because the pig- r ent of colored individuals acts as a filter, 7 to 8 ml. of the dye is necessary in such p tients.

As the Decholin method[16, 17] is one of the most widely used methods for the determination of the circulation time, we compared this method with the dermofluorographic method. The Decholin time is a subjective test, depending upon the perception of a bitter taste, after the injection of 5 ml. of 20 per cent sodium dehydrocholate (Decholin) into an antecubital vein. The recent advocation of the saccharin method,[18] which utilizes the perception of a sweet taste after the injection of 2.5 Gm. of saccharin in 4 ml. of distilled water, prompted us also to compare the accuracy of this method with that of the dermofluorograph.

Method

All tests were carried out after bed rest of at least 30 minutes.

In 5 patients, the relation between arm-to-tongue and arm-to-cheek times was first observed by means of the dermofluorograph with the search unit placed first on the tongue and 5 minutes later on the cheek. The results were within 0.5 second of each other, demonstrating that arm-to-cheek times were the equivalent of arm-to-tongue times.

In 100 patients, dermofluorographic and Decholin circulation times were determined. Sixty-two patients suffered from heart disease, (recent or old myocardial infarction, rheumatic or arteriosclerotic heart disease); 66 were over 65 years of age. In 60 patients, the objective method was performed first and was followed within 1 to 2 minutes by the injection of 5 ml. of Decholin through the same 20-gage needle at the same speed as the fluorescein; the Decholin time was accurately charted on the recorder by pressing the footswitch of the instrument at the start of the injection and again when the patient gave the first sign of perception of the bitter taste of Decholin. In 40 cases, the Decholin test was performed first. The dermofluorographic method was then compared with the saccharin method in 34 patients by the same technic. Nineteen of these patients were under 65, and 15 were over 65 years of age.

Table 1.—*Comparison between Dermofluorographic and Decholin Circulation Times*

No. of patients	Dermofluorographic time (seconds) (Normal 13–17 secs.)	Results obtained with Decholin
1	9	9
3	12	12, 16, 17
5	13	18, 19, 22, 25, 31
7	14	17, 18, 18, 18, 22, 27, 27
14	15	15, 17, 18, 18, 19, 20, 21, 23, 23, 24, 24, 30, NR*, NR
14	16	16, 16, 18, 18, 18, 19, 20, 21, 21, 21, 22, 22, 22, 30
5	17	21, 21, 22, 22, 24
6	18	19, 20, 24, 28, 30, 35
6	19	21, 26, 28, 29, 30, 40
3	20	21, 22, 42
4	21	25, 31, 39, 54
4	22	26, 28, 28, 48
3	23	23, 23, 31
3	24	27, 33, 35
2	25	27, 47
1	26	38
2	27	30, 32
1	28	54
2	30	32, NR
2	31	33, 48
1	33	45
2	34	44, 58
1	38	NR
3	40	40, 63, NR
1	41	NR
1	42	63
1	44	52
1	46	NR
1	47	NR

* NR = No response.

Results

The normal dermofluorographic arm-to-cheek time in adults is 13 to 17 seconds. In 49 patients with normal dermofluorographic circulation times, the Decholin time was on the average 37.5 per cent longer; in 44 patients with prolonged objective circulation times (over 17 seconds), the Decholin time averaged 47.5 per cent longer. There were 7 per cent "no responses" to Decholin in this series. In only 8 per cent of patients was the Decholin time equal to the dermofluorographic time. In 25 patients with normal

TABLE 2.—*Comparison between Dermofluorographic and Saccharin Circulation Times*

No. of patients	Dermofluorographic time (seconds) (Normal 13–17 secs.)	Results obtained with saccharin
1	10	15
1	11	20
3	13	18, 18, 19
2	14	19, 30
5	15	20, 20, 22, 24, 30
4	16	17, 20, 21, 22
9	17	21, 22, 25, 25, 26, 27, 28, 28, NR*
1	19	33
1	20	NR
1	21	35
1	25	46
1	27	42
1	28	29
1	29	NR
1	30	60
1	34	NR

* NR = No response.

objective times of the total group of 34 patients tested with saccharin and the dermofluorographic method, the saccharin time was on the average 48 per cent longer; in the 9 patients with prolonged objective times, the saccharin time averaged 64 per cent longer. There were 12 per cent "no responses" to saccharin in this group. None of the saccharin times was equal to the dermofluorographic time (tables 1 and 2).

DISCUSSION

Arm-to-tongue circulation times can be in error because the threshold of perception of taste by the tongue shows considerable individual variations. In addition, certain commonly used drugs, such as barbiturates, may alter the perceptive threshold considerably.[2]

In addition to the inherent errors in the subjective method, it appears that large residual cardiac volumes, such as are found in cardiac failure, tend to increase the error of the subjective method, since the dilution of the test substance becomes too great to be perceived immediately upon arrival at the test site. With the use of the subjective tests, it was often found that the degree of cardiac compensation and the velocity of blood flow did not bear a close relationship to each other,[19–22] i.e., although there was often no clinical evidence of cardiac decompensation the circulation time was prolonged. Nylin[23] suggested that cardiac enlargement per se could prolong the circulation time, because of the large amount of residual blood and the dilution of the test substance. Gernandt and Nylin[24] found a clear correlation between absolute and relative heart volume and the circulation time measured with Decholin. Meneely and Kaltreider[25] were also able to show a relation between circulation time and the size of the heart. Nathanson and Elek[2] showed that there was definite prolongation of circulation time as the size of the heart increased; they believed that the test substance was diluted and poorly mixed in a large cardiac chamber, so that there was delay in reaching the receptor organ in sufficient concentration. They also reasoned that since velocity varies inversely with the square of the radius, the speed of blood flow is actually slower through a large heart. In addition, the greater circulating blood volume in decompensation contributed to further dilution, so that the time for the threshold level to be reached is considerably prolonged.

It is well known that disagreeable tastes are perceived at much higher dilutions than sweet tastes.[27] The results obtained in this study show that the inaccuracy of the subjective method is increased by using a sweet taste as the end point (saccharin) instead of a bitter taste (Decholin).

The dermofluorograph is not only completely automatic and objective, but the instrument is capable of ascertaining a fluorescein concentration of 1 part in 30 million; thus the amounts injected far surpass the amounts needed for detection even under the most unfavorable circumstances. Amounts can be given that compensate by far for the additional dilution occurring in enlarged hearts. The method is repeatable, with an accuracy of ± 5 per cent. Fluorescein is a small molecular, readily available, inexpensive, nontoxic, nonallergenic brown dye; it

undergoes no change in the body and is rapidly and completely excreted, without chemical change, in the urine. In 0.1 per cent of about 2,000 cases studies, slight nausea or vomiting has occurred.

The present study demonstrates the superiority of the objective automatic dermofluorographic method of measuring circulation time over the subjective arm-tongue tests with Decholin or saccharin.

The values reported in tables 1 and 2 show that there is no constant relation between the objectively obtained dermofluorographic circulation times and the Decholin or saccharin circulation times. Thus the differences cannot be explained on the basis of slightly different ranges of normal. It must rather be stated that the errors of the Decholin and saccharin methods make the results obtained rather doubtful in their value for diagnosis and prognosis. This may be the explanation for many of the dubious results obtained in previous studies. Also, the unreliability of the subjective tests is increased in patients with enlarged hearts, especially in those with failure.

Summary

In 100 cases, a comparison study of the circulation time determined with Decholin and the fully objective dermofluorograph revealed a large (average 42.5 per cent) unpredictable error in the Decholin method.

In 34 cases, a comparison study of the saccharin and dermofluorographic circulation times showed that the saccharin time was less reliable than the Decholin time, with an even greater (56 per cent average) unpredictable error.

Decholin and saccharin circulation times are highly unreliable, especially in patients with failure. It appears that large residual cardiac volumes tend to increase the error of the methods.

The accuracy of the dermofluorographic method lies within ±5 per cent, and a circulation time with this instrument may be performed on unconscious patients, infants, and children, and surmounts all language barriers.

Summario in Interlingua

In 100 casos, un studio comparative del tempore circulatori determinate (1) per medio del methodo a Decholina e (2) per medio del totalmente objective methodo dermofluorographic revelava in le methodo a Decholin un grande e non-predicibile error que amontava a un valor medie de 42,5 pro cento.

In 34 casos, un studio comparative del tempore circulatori determinate (1) per medio del methodo a saccharina e (2) per medio del methodo dermofluorographic revelava in le methodo a saccharina un ancora plus grande error non-predicibile. Su valor medie esseva 56 pro cento.

Tempores circulatori determinate per medio del methodos a Decholina e saccharina es multo infidel, specialmente in patientes con disfallimento cardiac. Il pare que grande volumines residue in le corde tende a augmentar le error del methodos.

Le exactitude del methodo dermofluorographic se tene intra ±5 pro cento. Tempores circulatori pote esser determinate per medio del dermofluorographo in patientes in stato de inconscientia, in infantes, e in juveniles. Iste methodo es libere de omne barrieras linguistic.

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A patient with rheumatic heart disease is reported in whom there was embolization to the systemic arteries and in which the site of origin of the emboli was thought to be the smaller veins of the lungs. Many investigators in reporting the site of origin of systemic emboli in rheumatic heart disease have found a variable number of cases for which no intracardiac source can be demonstrated. The generally held belief, at present, that pulmonary veins are rarely the source of systemic emboli might have to be modified. It is suggested that a more careful dissection of the smaller pulmonary veins in such cases might reveal the source of the emboli.

Bernstein

Alimentary Lipemia and the Coagulability of Blood

Analysis by Thrombelastography and Silicone Clotting Time

By THOMAS W. SHEEHY, M.D., AND JAMES W. EICHELBERGER, JR.

The effect of alimentary lipemia on the coagulation of blood has been studied by means of thrombelastography as a new approach to this problem. Our observations revealed no acceleration of blood coagulation during the phase of alimentary lipemia by this method, which is one of the few technics capable of demonstrating a state of hypercoagulability.

THE effect of alimentary lipemia on coagulation has been a matter of controversy for most of the past decade. Reports have confirmed and denied an acceleration of whole blood coagulation.[1-10] A considerable amount of evidence is growing that purports to show lipemia as a factor in the pathogenesis of thrombotic disease, and perhaps even a factor in the genesis of atherosclerosis.[11] These speculations are based on the findings initially reported by Fullerton et al.[3] that the whole blood coagulation time in silicone is accelerated by alimentary lipemia. The vital importance of this problem led us to study it from a slightly different approach.

MATERIAL AND METHODS

Fifty normal soldiers who had recovered from various injuries and were about to be returned to duty participated in the experiment. They were divided into 3 groups: Group 1 (30 subjects) received a meal of eggs, bacon, butter, and toast containing altogether 100 Gm. of fat. Group II (10 subjects) received 250 ml. of 38 per cent cream. Group III (10 subjects) received 50 ml. of olive oil. Four samples of blood were drawn from each subject, 2 fasting and 2 postprandial.

The fasting samples were drawn at 30-minute intervals and the remaining samples were obtained 1 and 4 hours after the ingestion of the fatty material. The lipemic effect on coagulation following the ingestion of cream is maximum 1 hour after intake,[6] while solid fatty foods produce their maximum lipemic effect 3 to 4 hours after intake.[4]

Siliconized equipment was used throughout the study. Blood was taken from the antecubital vein with an 18-gage needle by use of the 2-syringe technic. A stopwatch was started as soon as blood entered the syringe. At least 8.0 ml. of blood were obtained and distributed as follows: 1.0 ml. was added to each of 2 10 by 100 mm. test tubes for the clotting time; 4.5 ml. were added to 0.5 ml. of 0.1 molar sodium oxalate to obtain platelet-rich plasma for thrombelastography and optical density determination, and 1.5 ml. was drawn into a calibrated tuberculin syringe. The latter was used to place 0.35 ml. of whole blood immediately into each of 3 cuvettes in the thrombelastograph. The time between entry of blood into the syringe and operation of the instrument was noted and added to the "R" value.

The silicone tubes were immediately placed in a water-bath at 37 C. Tube no. 1 was tilted at 5 minutes and every 3 minutes thereafter until the tube could be inverted without the flow of blood. At this point, tube no. 2 was inverted every 3 minutes until a similar end point was reached. The average of the 2 tubes was taken as the clotting time.

The thrombelastograph continuously records the process of coagulation and allows visual and photokymographic observation of the clotting of whole blood or recalcified plasma. The physical principles of the method and technical details have been described elsewhere and are presented briefly here.[12-16]

Three stainless steel cuvettes with nonwettable surfaces are mounted on thermostatically controlled bases that rotate through an arc of 4° 45′ every 9 seconds. A cylinder of similar material is suspended in the cuvette by a fine torsion wire. The small clearance of the latter from the sides and bottom of the cuvette (1.0 mm.) and the limited excursion of the cuvette reduce mechanical distortion of the clot to a minimum. Mounted on the torsion wire and reflecting the motion of the cylinder is a small mirror in direct line with a light source. Any motion imparted to the cylinder moves the mirror and deviates the light beam. The latter is stationary and recorded as

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TABLE 1.—*A Comparison of the Fasting and Lipemic Whole Blood Silicone Clotting Time Following the Ingestion of a 100-Gm. Fat Meal*

Subject	Fasting SCT (1) (min.)	Fasting SCT (2) (min.)	Lipemic SCT (1) (min.)	Lipemic SCT (2) (min.)
1	23.0	27.0	29.5	23.0
2	21.5	18.5	21.5	18.5
3	20.0	21.5	26.0	23.0
4	23.0	35.0	31.5	20.0
5	20.0	26.0	27.5	21.5
6	21.5	33.5	29.5	29.5
7	26.0	31.5	18.5	26.0
8	21.5	18.5	21.5	23.0
9	38.0	42.5	26.0	24.5
10	26.0	20.0	23.0	26.0
11	33.5	30.5	35.0	29.5
12	29.0	21.5	23.0	21.5
13	24.5	18.5	21.5	27.5
14	24.5	21.5	18.5	28.5
15	25.5	18.0	19.5	27.0
16	14.0	39.5	29.0	21.5
17	44.0	35.0	21.5	26.0
18	30.5	24.5	20.0	30.5
19	20.0	29.0	20.0	26.0
20	27.0	21.5	29.0	30.5
—	—	—	—	—
20	513.0	533.5	491.5	503.5
Mean:	25.65	26.67	24.58	25.18

Analysis of Variance

Source of variation (VS)	Degrees of freedom (DF)	Sums of squares (SS)	Mean squares (MS)	Variance ratio (F)
F1+F2 vs L1+L2	1	33.16	33.16	0.95
F1 vs F2	1	10.51	10.51	0.30
L1 vs L2	1	3.59	3.59	0.10
Error	76	2647.75	34.84	

a straight line on the moving photographic film (2 mm. per minute), prior to fibrin formation, but when fibrin begins to form, the cylinder is increasingly firmly bound to the cuvette, and the motion imparted to the cylinder indirectly deviates the light beam. In this manner fibrin formation is converted into the oscillation of a beam of light. As the formation of fibrin increases and progresses, the oscillations of the light beam increase in amplitude, and the magnitude of its sweep may be visually observed; at the same time its movement is outlined and recorded by the moving film (fig. 1).

A typical thrombelastogram is shown for comparison with several illustrating hypercoagulability and hypocoagulability (fig. 2*a, b, c, d,*).

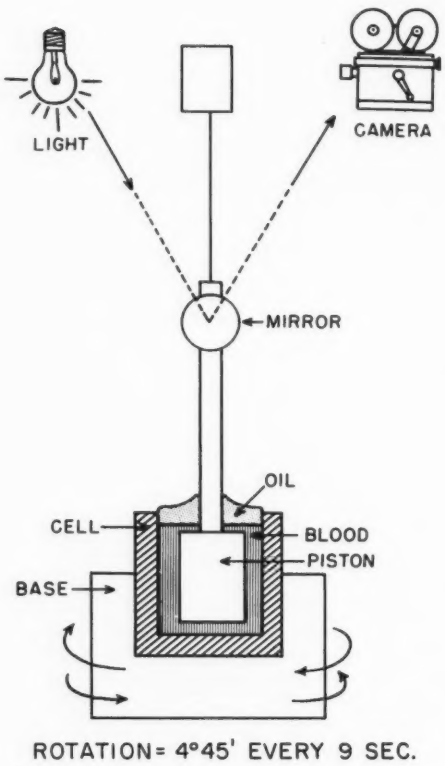

FIG. 1. Diagram of the thrombelastograph.

Three components of the coagulogram are of importance (fig. 3). The "R" (reaction) value represents the time required for fibrin formation to begin. Its end point is the point on the film where the *light* beam moves 1.0 mm. The "K" (coagulation) value is the distance from the end of "R" to the point where the divergent arms of the pattern are separated by a distance of 20 mm. This is the interval necessary for complete clot formation. The Ma (maximal amplitude) measures the elasticity of the clot. Increased coagulability is characterized by short "R" and "K" values with increased maximal amplitude, a pattern observed in over 80 per cent of patients with thrombosis.[17-18]

This instrument was utilized to study the effect of alimentary lipemia on coagulation, since it allows observation of the clot throughout coagulation. Fibrin formation, the basis of clot formation, can be observed from its initiation, and the "K" value provides a measurable end point for determining coagulation time. Thus, the instrument provides constants of motion, temperature, and clot reflection, all of which, when inconstant, interfere with the clotting time in a tube.

TABLE 2.—*A Comparison of the Fasting and Lipemic "R" and "K" Values of Thrombelastograms of Whole Blood and Silicone Clotting Times after Ingestion of 100 Gm. of Fat*

Subject	Fasting (1) (min.)		Fasting (2) (min.)		Lipemic (1) (min.)		Lipemic (2) (min.)	
	TEG	SCT	TEG	SCT	TEG	SCT	TEG	SCT
1	R 13.0 K 7.0 20.0	29.0	12.9 6.5 19.4	18.5	12.5 5.2 17.7	23.0	13.1 7.8 20.9	20.0
2	R 13.5 K 6.2 19.7	27.5	12.9 6.3 19.2	15.5	14.6 6.2 20.8	20.0	12.3 6.5 18.8	26.0
3	R 15.8 K 4.5 20.3	35.0	14.0 3.5 17.5	30.5	16.0 6.7 22.7	36.5	12.0 3.4 15.4	26.0
4	R 15.4 K 4.9 20.3	29.0	15.8 6.5 22.3	21.5	17.0 6.9 23.9	30.5	17.5 7.0 24.2	29.0
5	R 14.2 K 6.0 20.2	32.0	14.0 6.6 20.6	44.0	14.4 6.0 20.4	36.5	16.0 5.8 21.8	24.5
6	R 16.7 K 6.1 22.8	20.0	12.3 6.6 18.9	29.0	13.0 5.7 18.7	20.0	10.0 4.5 14.5	26.0
7	R 13.8 K 5.7 19.5	30.5	13.3 5.3 18.6	24.5	13.3 6.9 20.2	20.0	12.1 6.5 18.6	30.5
8	R 14.5 K 14.5 21.0	44.0	15.0 6.4 21.4	35.0	10.0 6.0 16.0	21.5	8.5 4.5 13.0	26.0
9	R 11.0 K 4.0 15.0	14.0	14.1 4.8 18.9	38.5	11.2 3.3 14.5	28.5	14.2 5.3 19.5	21.5
10	R 11.5 K 6.2 16.7	29.0	10.9 5.5 16.4	25.5	11.9 4.6 16.5	29.0	11.7 5.7 17.4	30.5
10	195.5	290.0	193.2	282.5	191.4	265.5	184.4	260.0
Mean	19.55	29.00	19.32	28.25	19.14	26.55	18.44	26.00

Analysis of Variance

VS	DF	TEG (R plus K)			SCT		
		SS	MS	F	SS	MS	F
F1+F2 vs L1+L2	1	4.15	4.15	0.50	55.22	55.22	1.07
F1 vs F2	1	0.27	0.27	0.03	2.82	2.82	.05
L1 vs L2	1	2.46	2.46	0.29	1.52	1.52	.03
Error	36	262.46	7.29		1861.40	51.71	

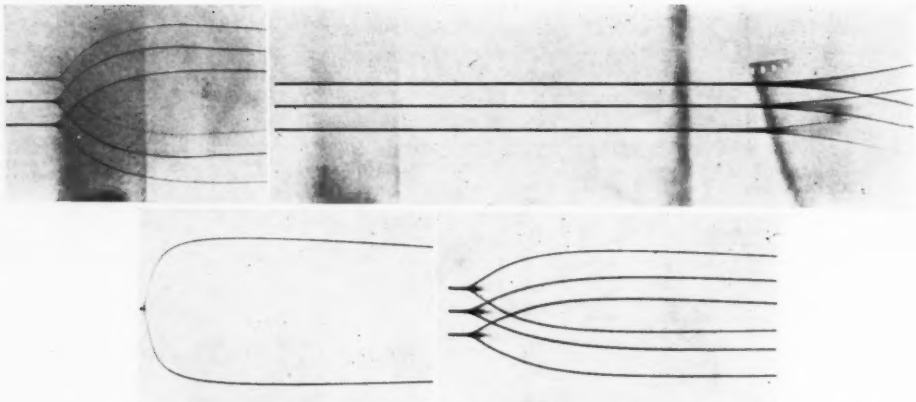

FIG. 2. Thrombelastographic patterns. *Top left.* Normal thrombelastogram of whole blood. R 10 minutes, K 6 minutes. *Top right.* Hemophilia. Whole blood—R 95 minutes, K 37 minutes. *Bottom left.* Hypercoagulability. R 90 seconds, K 60 seconds. *Bottom right.* Platelet deficiency.

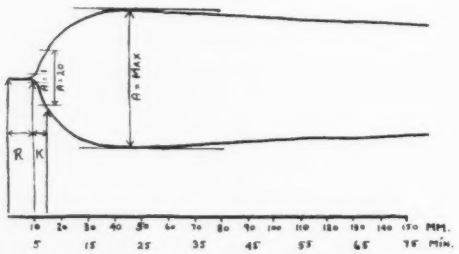

FIG. 3. A thrombelastogram.

Platelet-rich plasma was obtained by allowing the oxalated samples to stand for 30 minutes. The plasma thrombelastographs were made by filling each cuvette with 0.25 ml. of plasma, positioning the cylinders and at this point adding 0.1 ml. of 1.29 per cent calcium chloride. With the addition of calcium, a stop watch was started and the "R" and "K" values were obtained. Optical density determinations were made on a Coleman spectrophotometer at 650 mμ.

RESULTS

The results of the experiments are summarized in table form. Table 1 shows the silicone clotting times of 20 subjects prior to and after the ingestion of a fat meal (100 Gm.). No trend toward postprandial acceleration of coagulation was observed. Occasionally a marked difference in the clotting times was noted between the fasting samples or the lipemic samples, despite our efforts to keep variables within the test at a minimum and the patient at rest. Variation in the degree of the silicone coating of the tubes may have been responsible for this effect. The mean clotting time for the 80 observations was 26.55 ± 5.88 minutes, with a range from 14.0 to 44.0 minutes. Statistical analysis of the results revealed no significant change between the fasting and lipemic clotting time.

Table 2 contains the results of a study on 10 subjects who received the same type fat meal. Thrombelastographic values are portrayed with silicone clotting times which were done at the same time. Neither the "R" values, indicating the time fibrin formation began, or the "R" plus "K" time, indicative of clot formation of a certain elasticity, nor the silicone clotting time, appears affected by lipemia (figs. 4 and 5). Tables 3 and 4 contain similar observations before and after the ingestion of cream and olive oil. No significant effect on the coagulation of whole blood was observed. Observations of recalcified plasma on the thrombelastograph likewise revealed no evidence of change when lipemic plasma was utilized. Lipemia was excellent with cream and the fat meal, but after the ingestion of olive oil the plasma changed little in appearance although the average change in optical density at 4 hours exceeded 0.1 unit.

TABLE 3.—*A Comparison of the Fasting and Lipemic "R" and "K" Values of the Thrombelastograms of Whole Blood and Silicone Clotting Times (Subjects ingested 250 ml. of 38 Per Cent Cream)*

Subject	Fasting (1) (min.)		Fasting (2) (min.)		Lipemic (1) (min.)		Lipemic (2) (min.)	
	TEG	SCT	TEG	SCT	TEG	SCT	TEG	SCT
1	R 13.8 K 5.0 18.8	26.0	10.2 5.2 15.4	21.5	13.3 5.0 18.3	24.5	14.8 5.3 20.1	27.5
2	R 13.3 K 4.5 17.8	29.0	13.0 4.0 17.0	27.5	12.2 5.3 17.5	26.5	12.8 6.3 19.1	29.5
3	R 11.0 K 5.5 16.5	23.0	15.0 6.0 21.0	42.5	16.0 6.5 22.5	21.5	12.0 5.4 17.4	23.0
4	R 13.7 K 5.0 18.7	23.0	12.2 5.0 17.2	20.0	13.3 5.1 18.4	18.5	14.6 5.3 19.9	14.0
5	R 11.6 K 5.4 17.0	36.5	11.5 5.5 17.0	38.0	11.2 5.6 16.8	32.0	11.8 7.5 19.3	29.0
6	R 11.2 K 5.3 16.5	15.5	11.4 5.4 16.8	23.0	9.3 4.5 13.8	18.5	11.6 6.0 17.6	20.0
7	R 15.0 K 6.0 21.0	23.0	14.3 4.9 19.2	39.5	15.8 6.5 22.3	47.0	18.0 6.3 24.3	32.0
8	R 11.2 K 6.0 17.2	24.5	11.1 4.5 15.6	23.0	11.4 4.1 15.5	20.0	12.0 5.5 17.5	23.0
9	R 14.8 K 5.0 19.8	35.0	13.9 2.5 16.4	30.5	16.1 6.6 22.7	36.5	11.5 4.0 15.5	26.0
10	R 13.5 K 6.1 19.6	26.5	12.8 6.6 19.4	18.5	14.6 6.2 20.8	20.0	12.7 6.5 19.2	26.0
Sum	182.9	262.0	175.0	284.0	188.6	265.0	189.9	250.0
Mean	18.29	26.20	17.50	28.40	18.86	26.50	18.99	25.00

Analysis of Variance

VS	DF	TEG (R plus K)			SCT		
		SS	MS	F	SS	MS	F
F1+F2 vs L1+L2	1	10.61	10.61	2.04	24.1	24.1	0.42
F1 vs F2	1	3.12	3.12	0.60	24.1	24.20	0.42
L1 vs L2	1	0.09	0.07	0.01	11.25	11.25	0.20
Error	36	187.30	5.20		2073.00	57.58	

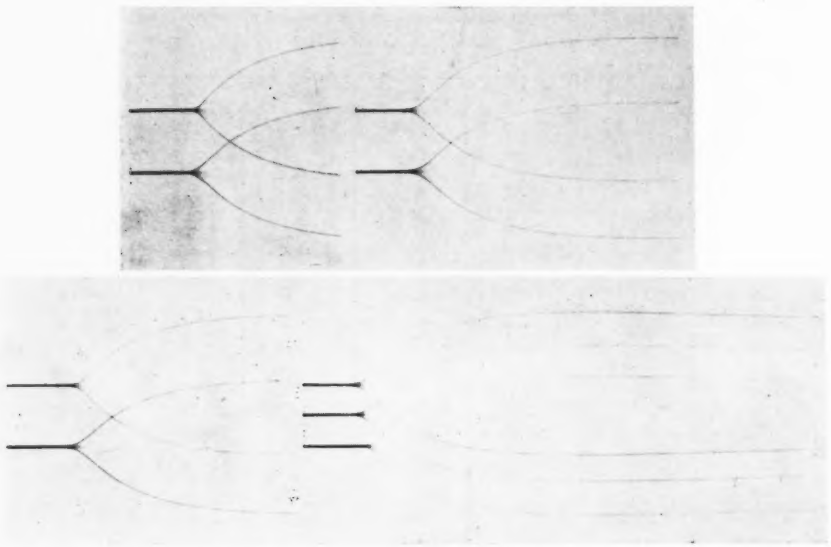

FIG. 4. Whole blood thrombelastograms. *Top.* Fasting samples at half hour intervals. Duplicate determinations. *Bottom.* Lipemic samples at 1 and 4 hours postprandial. Duplicate and triplicate determinations.

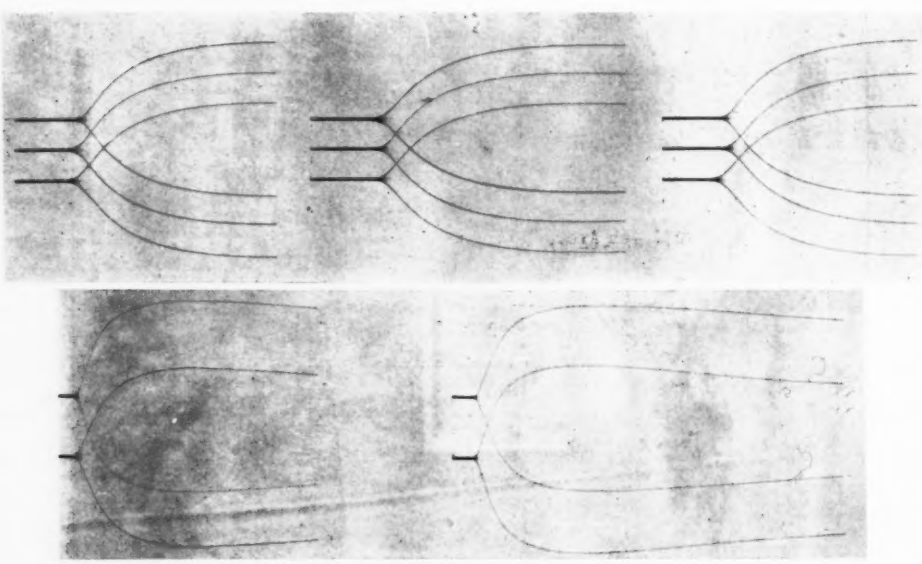

FIG. 5. *Top.* Whole blood thrombelastograms. Fasting sample (*left*); lipemic sample, 1 hour postprandial (*center*); lipemic sample, 4 hours postprandial (*right*). *Bottom.* Plasma thrombelastograms. Fasting (*left upper*); fasting 30 minutes later (*left lower*); lipemic, 1 hour postprandial (*right upper*); lipemic, 4 hours postprandial (*right lower*).

TABLE 4.—*Comparison of the "R" Plus "K" Values of the Thrombelastograph and the Silicone Clotting Times of Whole Blood Following Ingestion of 50 ml. of Olive Oil*

ubject	Fasting (1) (min.)		Fasting (2) (min.)		Lipemic (1) (min.)		Lipemic (2) (min.)	
	TEG	SCT	TEG	SCT	TEG	SCT	TEG	SCT
1	R 12.3 K 5.2 17.5	(27.5)	14.0 6.5 20.5	36.5	13.0 5.5 18.5	29.0	13.3 5.3 18.6	30.5
2	R 12.3 K 4.0 16.3	18.5	12.3 3.3 15.6	18.5	11.0 4.3 15.3	27.0	12.0 4.7 16.7	32.0
3	R 13.5 K 6.0 19.5	26.0	11.5 5.5 17.0	24.5	11.0 5.5 16.5	20.0	13.0 6.2 19.2	27.5
4	R 13.0 K 6.5 19.5	20.0	11.5 6.4 17.9	21.5	12.0 5.5 17.5	27.5	11.3 4.5 15.8	18.5
5	R 13.5 K 4.8 18.3	27.5	13.0 4.3 17.3	42.0	15.0 6.0 21.0	20.0	15.5 5.2 20.7	36.0
6	R 12.3 K 4.6 16.9	21.5	12.0 5.0 17.0	18.0	12.2 4.8 17.0	23.0	11.6 4.5 16.1	33.5
7	R 12.5 K 5.5 18.0	26.0	13.1 5.5 18.6	35.0	13.8 5.0 18.8	29.0	14.0 6.4 20.4	32.0
8	R 11.4 K 6.0 17.4	20.0	11.2 5.8 17.0	27.5	11.7 6.5 18.2	24.5	11.1 5.3 16.4	24.5
9	R 11.5 K 5.0 16.5	21.5	12.3 5.2 17.5	29.0	11.4 5.3 16.7	35.0	12.0 5.1 17.1	29.0
10	R 13.2 K 4.8 18.0	26.0	13.0 5.5 18.5	24.5	12.8 5.0 17.8	26.0	13.4 4.8 18.2	27.5
Sum	177.9	234.5	176.9	277.0	177.3	261.0	179.2	291.0
Mean No.	10 17.79	23.45	10 17.69	27.70	10 17.73	26.10	10 17.92	29.10

Analysis of Variance

VS	DF		SS		MS		F	
	TEG	SCT	TEG	SCT	TEG	SCT	TEG	SCT
F1+F2 vs L1+L2	1	1	0.07	41.0	0.07	41.0	0.03	1.35
F1 vs F2	1	1	0.05	90.32	0.05	90.32	0.02	2.99
L1 vs L2	1	1	0.18	45.0	0.18	45.0	0.08	1.49
Error	36	36	76.58	1092.6	2.13	30.35		

Discussion

Our study revealed no significant alteration of the whole blood coagulation time during alimentary lipemia, either by the silicone clotting technic or thrombelastography. Our observations do not contradict the original observation of MacFarlane and associates[19] on the shortening of the "Stypven" (Russell's viper venom) clotting time of recalcified plasma. This observation has been confirmed by others.[20] However, incomplete (fat-free) thromboplastins, such as Stypven, require the addition of a "lipid" factor for activitation.[21] Sohar et al.[8] notes that the Stypven prothrombin time is reduced when there is an elevation of trigylcerides, and Poole thinks the chylomicrons are responsible.[20-22]

Sohar et al., however, could not find an acceleration of the whole blood clotting time during alimentary lipemia and believes, as we do, that it is too crude a test to detect acceleration of coagulation during alimentary lipemia. The thrombelastograph is capable of detecting hypercoagulability, as previously noted, and at the present time it is the only practical method of determining the hypercoagulability of whole blood or plasma. Our observations agree with those of Manning and Walford[7] and Tulloch and co-workers,[5] and are at variance with those of O'Brien[4] and Keys et al.[10]

Summary

The whole blood silicone clotting time of 20 normal males, fed a 100 Gm. fat meal, was *not* shortened during alimentary lipemia.

Three groups of normal men (10 in each group) received either a 100-Gm. fat meal, 250 ml. of 38 per cent cream, or 50 ml. of olive oil. In none of these groups did the whole blood silicone clotting time or the whole blood or plasma thrombelastograms show acceleration during alimentary lipemia.

Acknowledgment

The authors wish to express their gratitude to Col. W. H. Crosby for his aid and guidance in this project.

Summario in Interlingua

Durante le lipemia alimentari, inducite 1 20 masculos normal per un repasto de 100 g de grassia, specimens de sanguine integre n monstrava un reducite tempore de coagul - tion a silicona.

Tres gruppos de 10 masculos normal ca un recipeva un repasto de 100 g de grass o de 250 ml de 38 pro cento de crema o 5 ml de oleo de oliva. Nulle de iste grupp monstrava durante le lipemia alimentari u acceleration del coagulation a silicona co sanguine integre o del thrombelastogramma con sanguine integre o plasma.

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Cooley, D. A., Belmonte, B. A., Zeis, L. B., and Schnur, S.: Surgical Repair of Ruptured Interventricular Septum Following Acute Myocardial Infarction. Surgery **41**: 930 (June), 1957.

Five days following an acute myocardial infarction, a 49-year-old man developed signs and symptoms compatible with rupture of the interventricular septum. This complication was confirmed by cardiac catheterization 9 weeks later. Following the perforation of the septum, congestive heart failure appeared and remained a persistent problem, despite a rigid cardiac regimen. Eleven weeks after the perforation, surgical closure of the septal defect was effected through a right ventriculotomy incision and by use of extracorporeal circulation. The defect was approximately 6 cm. in diameter. Repair was accomplished with black silk sutures and polyvinyl sponge. The patient improved remarkably for about 4 weeks following surgery, despite persistence of a soft precordial systolic murmur over the lower sternum. This murmur began to increase in intensity approximately 4 weeks postoperatively. Separation of the sternal wound necessitated a secondary closure. Cardiac failure recurred 6 weeks postoperatively and the patient died a few days later. Autopsy disclosed a healed cardiotomy incision with the polyvinyl sponge still attached in the septal defect but 1 suture had torn out leaving a 0.5 cm. interventricular opening. On the basis of the experience in this patient, the authors speculate that rupture of the interventricular septum as well as other complications of myocardial infarction, such as ventricular rupture with pericardial tamponade, ventricular aneurysm, and ruptured papillary muscle, may prove to be amenable to surgical treatment.

BROTHERS

Further Experiences with Blood Coagulation after Fat Meals and Carbohydrate Meals

By JAIME BORRERO, M.D., ERWIN SHEPPARD, PH.D., AND IRVING S. WRIGHT, M.D.

There have been conflicting reports as to whether the ingestion of fat increases the tendency for the blood to clot, and hence, by implication, the risk of thromboembolic complications in man. In this study the effect of a single meal containing a large amount of fat was compared with that of a practically purely carbohydrate isocaloric meal. Under carefully controlled conditions the clotting time varied widely under fasting conditions, and after both fat and carbohydrate meals the clotting time became longer, shorter, or remain unchanged. The results were unpredictable and although a slight trend toward shortened clotting times was evidenced after the fat meals, the results did not reach accepted statistical standards of probability.

IN 1949 Duncan and Waldron[1] reported an acceleration of blood clotting time after the oral administration of fat. An original report from this department[2] casts doubt on this finding and it was suggested that the acceleration of clotting may well have been due to deposition of thrombin on the surface of glass syringes when they were reused for successive venipunctures. Then Waldron and Duncan published data that they believed substantiated their original claims.[3]

Buzina and Keys,[4] working with physically healthy men, aged 35 to 60, and using a larger amount of fat, reported a significant shortening of the whole blood coagulation time but no alterations after the ingestion of isocaloric, nonfatty meals. English workers[5-12] have reported on different aspects of this problem.

Hall[5] related clotting variations after a fat meal to platelet preservation and stated that there was no change in blood coagulation when adequate platelet activity was present.

Barkhan, Newlands, and Wild[6] have isolated from human brain tissue a phosphatidylethanolamine that they found to be an accelerator of coagulation. O'Brien[9] believes that behavior of phosphatidylethanolamine and platelets is similar. Studying further the effects of eggs and different fats on blood coagulation,[11] he found a shortening of Stypven clotting times 1½ to 2½ hours after a meal. There were considerable differences among individuals but no significant differences among different types of fat meals. There is some question whether the Stypven clotting time may actually be measuring the fat in the blood rather than an actual change in the clotting mechanism.

MacLagan and Billimoria[12] reported definite shortening of the clotting time after feeding 2 ounces of fat food, the maximal effects taking place 4 to 6 hours after a test meal.

Because of the opposing conclusions reached by different investigators and because Buzina and Keys[4] believed they found statistically significant support of acceleration of clotting times with a fat meal after re-analysis of the data of Tulloch, Overman, and Wright,[2] it was decided to try to reproduce as closely as possible the work of Buzina and Keys and to evaluate the results.

METHODS

Blood was withdrawn from an arm vein with siliconized syringes and 20-gage needles. If there was any difficulty in obtaining blood, a new venipuncture was done in the opposite arm with a new needle and a new syringe. A stopwatch was started as soon as blood entered the syringe. The tourniquet was kept in place no more than 60 seconds. One milliliter of blood was added to

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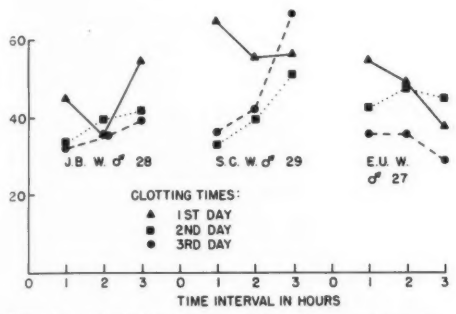

FIG. 1. Variation of clotting times under fasting conditions.

each of 4 siliconized tubes previously kept in a water bath at 37 C.

For the whole-blood clotting time, 1 of the siliconized tubes was tilted every 60 seconds starting at the end of 9 minutes from the time of blood withdrawal until clotting occurred, at which time tilting of the second tube was similarly started. When clotting occurred in the second tube, tilting of the third and fourth tubes was started simultaneously, and the average clotting time for the third and fourth tubes (computed from the time of blood drawing) was taken as the final clotting time.

The studies were conducted in 3 separate series. 1. Three healthy males, aged 27, 28, and 29 years, were tested in the fasting state. Blood was drawn and clotting time determined according to the above technic, and repeated twice in the same morning at hourly intervals. Nothing was taken orally throughout the experiment. This test was repeated twice on different days for each individual. The object of this series of tests was to determine the variations of clotting times in the same individual from test to test on the same day without food and also on different days. 2. Nineteen healthy individuals, aged 19 to 30 (13 men and 6 women) were then tested. The subjects ingested a test meal of 300 ml. of 40 per cent butterfat cream totaling 1,080 calories after the control blood samples were withdrawn. Blood samples were drawn at 1.0, 2.0, 3.5, 4.5, and 5.5 hours after the meal. According to Buzina and Keys' routine, the experiments were repeated with the same subjects, after a meal that provided 964 calories but only 0.15 Gm. of fat. This low-fat, high-carbohydrate meal consisted of cooked rice, table syrup, grape juice, lactose, and marshmallows. 3. Finally, 10 individuals, aged 35 to 70, were tested in the same manner with the fat meal and the carbohydrate meal.

RESULTS

Recorded in figure 1 are the clotting times measured under fasting conditions. The variation for clotting times in the same individual during the same day ranged from 7 minutes to 31 minutes between the first and the third sample. Variations in the same individual for different days ranged from 20 minutes to 33 minutes. In contrast with the report of Buzina and Keys, our clotting times during continued fasting were either longer or shorter than the initial one.

TABLE 1.—*General Statistical Analysis*

	Hours				
	1	2	3.5	4.5	5.5
Mean Fat-carbohydrate	+0.310	+5.414	+0.828	−2.378	+3.621
S.E.	2.748	3.221	2.814	3.038	2.507
t	0.113	1.681	0.294	0.783	1.444
p	N.S.	N.S.	N.S.	N.S.	N.S.

tp 0.1 = 1.70, tp 0.05 = 2.05, tp 0.01 = 2.76.
N.S. = No significance.

Table 1 shows the summary of our experiments and the statistical analysis. Because of the variations found in fasting clotting times, the following steps were used to calculate the mean values.

The variation of clotting times of samples from each individual were calculated first after fat meals and then after carbohydrate meals, by subtracting the values found at the 1, 2, 3.5, 4.5, and 5.5 hours from the corresponding fasting value. Plus (+) signs indicate shortening and minus (—) signs lengthening. When the + or — variations were calculated for the whole group, the mean was found for the values at the 1, 2, 3.5, 4.5, and 5.5 hour levels after the test meals and the difference between the fat and carbohydrate values was calculated.

Because no appreciable difference was found in the age groups of 19 to 30 and 35 to 70, the experiments were analyzed to include a total of 29 patients. Statistically significant acceleration of the clotting times after a high-fat meal was not found. The maximal effect was at the end of the second

TABLE 2.—*Fat Action on Blood Clotting: Average Response at 3½-4½-5½ Hours*

Change	Fat			
	Positive	Unchanged	Negative	Total
Positive	5	4	3	12
Unchanged	4	5	2	11
Negative	5	1	0	6
Total	14	10	5	29

Sign test for fat action, +3.36; sign test for carbohydrate action, +1.36.

hour but this did not reach the 10 per cent level of statistical probability.

Our next step was to analyze the data by means of a paired contingency table. For the contingency table the responses were classified as positive, negative, or unchanged. The designation "unchanged" did not mean that the readings were identical but rather that they fell within the limits of variation inherent in the technic. The inherent variation, determined from the differences between duplicates, was found to be approximately plus or minus 4 minutes.

Table 2 shows the results with the average responses at 3.5, 4.5, and 5.5 hours after meals. After a fat meal the blood of 14 individuals showed a positive response, i.e., a decrease in clotting times, and 5 an increase or negative response. After the isocaloric carbohydrate meal, a total of 12 individuals had a positive response (shortening) and 6 a negative one (lengthening). A sign test was applied to the results, for both fat and carbohydrate, those individuals being disregarded whose clotting times were unchanged by their test meals when compared to their fasting times.

Here again there was no statistically significant difference between the changes induced by fat and those produced by carbohydrate. As in our original statistical presentation (table 1), the sample that showed the nearest approach to statistical significance was at the second hour. The results with a paired contingency table were also analyzed (table 3). A total of 16 patients showed a decrease in clotting times following a fat meal. Four showed an increase.

TABLE 3.—*Fat Action on Blood Clotting—Second Hour*

Change	Fat			
	Positive	Unchanged	Negative	Total
Positive	5	4	1	10
Unchanged	4	1	2	8
Negative	7	3	1	11
Total	16	9	4	29

Sign test for fat action, +6.05; sign test for carbohydrate, +0.36.

Following carbohydrate meals, 10 showed a decrease compared with their fasting clotting times and 11 an increase. In this experiment the sign test showed a statistical significance between the 5 per cent and the 1 per cent level after the fat meal. The apparent discrepancy between the statistical data in table 1 and table 3 is a function of the characteristics of the different tests employed. Table 1 presents the results of analysis by means of the t test, a measure of degree of change. In table 3 the data presented are the result of application of the nonparametric sign test, a measure of direction of change only. Thus table 1 represents a slightly more efficient evaluation and while the values at the end of 2 hours approach significance, the criteria of significance are not achieved. When the first series of individuals, 19 to 30 years old, were tested, heparin tolerance tests, Stypven clotting times, prothrombin times, and thrombin generation tests were done in the first 10 individuals but abandoned thereafter because no changes were found.

DISCUSSION

Because of the important and controversial issue involved, special care was taken in the conduction of the present study. Subjects were selected for their willingness to cooperate and the presence of good veins suitable for adequate venipuncture.

The small group of 10 subjects aged 35 to 70 were ambulatory hospital cases, without evidence of metabolic disturbances, liver disease, gastrointestinal pathology, or renal

disease. They were included in the general group because it was found that they showed the same response after fat and carbohydrate tests meals as that of the younger group composed of medical and nursing students.

There was a great variability in the fasting clotting times among subjects and also in the same subject for different samples in the same day and for different days.

We agree with O'Brien,[10] that there is considerable difference among individual responses to a fat meal just as there is in responses to a carbohydrate meal.

The maximal shortening of coagulation time after a meal was found to occur at the end of 2 hours after the test meal. Comprehensive statistical analysis demonstrated that this showed only a 10 per cent rate of probability. This is below the limits of statistical standards and cannot be accepted as a demonstration of significant response.

Summary

The results of studies of changes in the coagulation time after a fat and a carbohydrate test meal ingested by 29 subjects are presented. It was found that the whole blood clotting times in siliconized tubes following the Lee-White method as modified by Buzina and Keys varied from individual to individual and in the same subject during the course of one day and from one day to another. Although there seems to be a slight trend toward shortening of clotting times following a standard fat meal, the results do not reach accepted statistical standards of probability. These experiments fail to confirm or deny the claim that fat ingestion accelerates to a significant or consistent degree the whole blood clotting time. A similar inconclusive trend toward shortening of the clotting time was observed following the ingestion of a carbohydrate meal in a substantial proportion of the tested individuals. Additional studies including the Stypven clotting time, heparin tolerance, prothrombin time, and thrombin generation, failed to show any trend toward increased speed of clotting. While these studies fail to demonstrate that the ingestion of a meal containing a large amount of fat encourages intravascular clotting, it is recognized that all existing methods of investigation of this mechanism are relatively crude and that such a possibility exists through a system not yet discovered.

Acknowledgment

The authors wish to thank Dr. Irwin D. J. Bross, Assistant Professor of Biostatistics, Department of Public Health and Preventive Medicine, Cornell University Medical College for his aid in the statistical analysis of this material. Acknowledgment is made to Mrs. Lorraine Rose and Miss Ann Florio for their technical assistance in carrying on this work.

Summario in Interlingua

Es presentate le resultatos de studios relative al alterationes del tempores de coagulation post repastos experimental de grassia e de hydratos de carbon ingerite per un serie de 29 subjectos. Esseva constatate que le tempores del coagulation de sanguine integre in tubos a revestimento de silicona, determinate secundo le methodo de Lee-White in un modification per Buzina e Keys, variava ab un individuo al altere e in le mesme individuo ab un die al altere e in le curso del mesme die. Ben que il pare exister un leve tendentia verso accelerate tempores de coagulation post repastos standard a grassia, le resultatos non satisface le acceptate standards statistic de probabilitate. Iste experimentos non confirma e non denega le assertion que le ingestion de grassia accelera a grados significative e de maniera uniforme le coagulation de sanguine integre. In un proportion considerabile del individuos studiate, un simile tendentia inconclusive esseva observate in le acceleration del coagulation post le ingestion de repastos a hydratos de carbon. Studios additional—incluse le tempore coagulatori de Stypven, le tolerantia de heparina, le tempore prothrombinic, e le generation de thrombina—non revelava ulle tendentia verso un acceleration del processo coagulatori. Durante que iste studios non demonstra que le ingestion de repastos a alte contento de grassia promove le coagulation intravascular, il debe esser recognoscite que omne le exist-

ente methodos pro le investigation de iste mechanismo es relativemente crude. Il remane possibile que le phenomeno in question va esser demonstrate per medio de un systema non ancora discoperite.

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Van Buchem, F. S. P., Nieveen, J., and Van der Slikke, L. B.: The Diagnosis of Myxoma Cordis. Diagnosis Established Pre-operatively in Two Cases. Cardiologia **30**: 353 (June), 1957.

The diagnostic features of myxoma of the left atrium are discussed and illustrated by the histories of 2 patients recognized during life and confirmed by surgery and autopsy. Characteristic findings include a past history of variable signs and symptoms, readily influenced by changes in posture and rapid progression of heart failure not responding to the usual therapy. Fluoroscopically forceful esophageal pulsations may be observed at the level of the left atrium. If the atrial tumor is large enough, cardiac catheterization reveals pressure elevation in the right ventricle and in the pulmonary artery. In the pulmonary wedge-pressure curve an early positive deflection replaces the normal dip during ventricular systole. Finally angiocardiography reveals a filling defect within the shadow of the atrium.

Pick

Primary Aortic Thrombosis

By H. Gaylis, Ch.M., F.R.C.S.

Primary arterial thrombosis is a rare lesion and may be defined as thrombosis of a vessel without any obvious underlying cause. The condition has been described in the peripheral arteries of the upper and lower extremities but there are few authenticated reports of the condition affecting the aorta. A case of primary aortic thrombosis occurring in a man aged 32 is reported.

THROMBOSIS of the terminal aorta, insidious in onset and progress, is not uncommon. Since 1940 the clinical picture has been made clear, largely owing to the communications of Leriche and Morel.[1] The clinical features originally described by Leriche were (1) in the male, inability to maintain a stable erection because of a reduced blood flow through the internal pudendal arteries; (2) extreme fatigability of the lower limbs when walking or standing; (3) generalized atrophy of muscles in both buttocks and in both lower limbs; (4) absence of nutritional changes of the skin and pallor of the feet when the patient was standing. Since then it has been recognized that claudication of the calf muscles is the usual presenting symptom and that nutritional changes proceeding to gangrene may occur. Most cases of aortic occlusion occur in males in the fifth and sixth decades, but the condition has been reported in patients as young as 29 years.[2]

In the vast majority of instances the thrombosis is secondary to atherosclerosis or embolism. Less commonly, thrombosis may occur in the sac of an aneurysm of either the dissecting or saccular type and has followed syphilitic aortitis,[3] pressure by tumors,[4] pelvic peritonitis, and irradiation to the abdomen. The following description of a case of aortic thrombosis occurring in a young adult man is of interest because the thrombosis was primary in origin, a rare event.

Case Report

A 32-year-old married man was admitted on December 11, 1955, complaining of a feeling of tightness in the right calf, precipitated by walking 50 yards and relieved by rest. The onset of this symptom was gradual and had been present for 5 months. Systematic inquiry revealed that during this period he had increasing difficulty in sustaining an erection. Apart from the usual childhood illnesses the past history was noncontributory. He smoked 3 or 4 cigarettes a day and only occasionally took alcohol.

On examination his general condition appeared good and there was no evidence of anemia. The blood pressure was 140/90 mm. Hg, and the pulse was 80 and regular. The heart was clinically normal and the fundi showed no abnormalities. The major pulses in both upper limbs were present and equal and the arterial walls were soft.

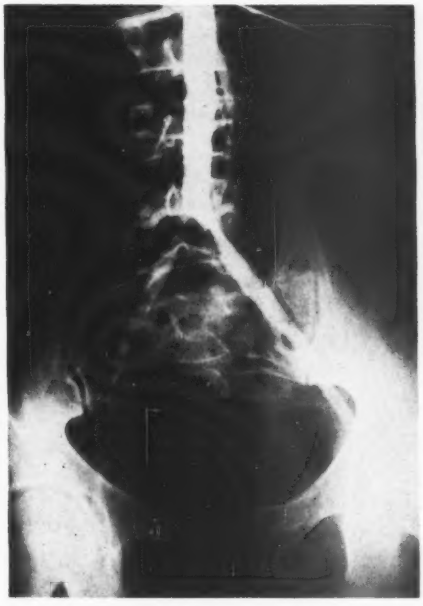

Fig. 1. Percutaneous translumbar aortogram showing a filling defect of the aortic bifurcation and affecting the right common iliac artery more than the left.

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FIG. 2. The excised terminal aorta and common iliac arteries. The thrombosis was more extensive than indicated by aortography.

The skin nutrition of the lower extremities was good, the plantar surface of the feet showed no pallor on elevation or congestion on dependency. There was no decrease in muscle mass or increased venous filling time. The skin temperature was normal. The femoral pulses were decreased, the popliteal pulses doubtfully present or absent, and the post-tibial and dorsalis pedis pulsations were absent.

The lungs, abdomen, and central nervous system were clinically normal. Because of diminution of the femoral pulses and the inability to maintain an erection, a diagnosis of aorto-iliac obliterative arterial disease was made.

The hemoglobin was 15.9 Gm. per cent, the white blood cell count was 14,000 per mm.^{3}, the Wassermann and Kahn tests were negative, the blood urea nitrogen was 31 mg. per cent, and the serum cholesterol was 286 mg. per cent. Urinalysis showed no albumin or glucose. An electrocardiogram and x-ray of the heart and lungs were normal.

A percutaneous lumbar aortogram (fig. 1) revealed a filling defect at the aortic bifurcation and affecting the right common iliac artery more than the left. The appearances were suggestive of extraneous pressure but were consistent with atherosclerosis. The aorta and the iliac arteries adjacent to the affected segment showed no evidence of obvious atheroma. In view of the disabling nature of his symptoms and the localized

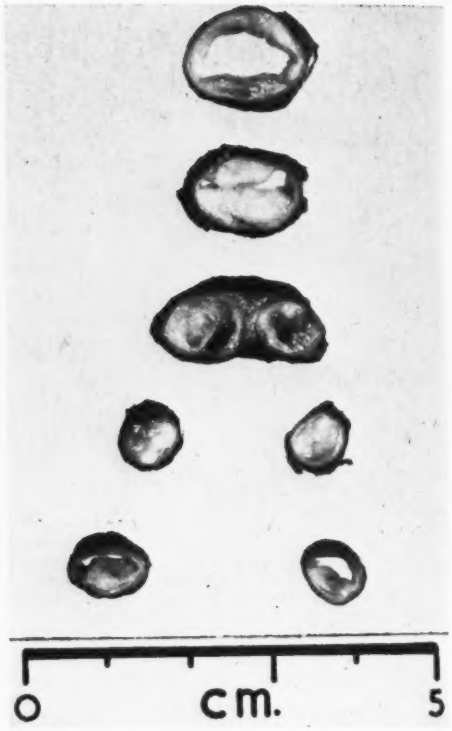

FIG. 3. A series of transverse sections from different levels showing the site and degree of narrowing.

pathology of the disease, the lesion was considered ideal for resection and grafting.

Through a long left paramedian incision the lower abdominal aorta and common iliac arteries were exposed. The external appearances of these vessels were normal, but palpation revealed marked induration of the aortic bifurcation. The inferior mesenteric, fourth lumbar, and presacral arteries having been ligated and divided, arterial clamps were placed on the aorta below the renal arteries and on both common iliac arteries distal to the diseased vessels. Mobilization and excision of the affected segment was easy in contrast to that usually encountered with atherosclerotic vessels. The thrombosed segment was more extensive than that indicated by aortography and palpation. Figure 2 is a photograph of the excised aorta-iliac segment and figure 3 shows the specimen incised transversely at different levels to show the extent of thrombosis. Continuity was restored by a prefabricated polyvinyl alcohol sponge prosthesis that was sutured in place with 0000 arterial sutures with a continuous over-and-over suture

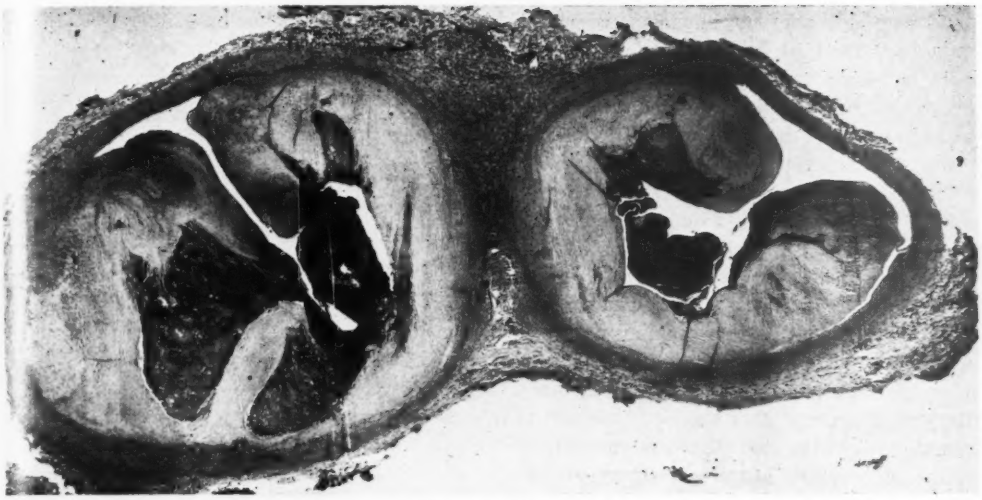

FIG. 4. Transverse section just below the aortic bifurcation. The pale staining fibrous organization and the dark staining recent thrombus can be clearly distinguished. Note the unaffected parts of the wall in the upper and out quadrants. (H and E × 9)

The postoperative course was uneventful. All the major pulses in the lower extremities returned and were normal and equal. The claudication disappeared and he was later able to report that his sexual functions were normal.

The following is the pathologic report on the excised specimen by Professor C. V. Harrison:

"The specimen is shown in figure 2. It was further cut into a series of transverse slices of which a selection is shown in figure 3. The site of the maximal narrowing was at the bifurcation of the aorta but even here obliteration was not quite complete (fig. 4). Microscopically there is evidence of organizing or organized thrombus at every level and in all sections this affects only part of the circumference, leaving at least a small segment free. The fibrous organization was in layers, indicating that it occurred in episodes. In most of the sections some unorganized thrombus is present. In most cases this is superficial (fig. 4), but sometimes it is deeper. All these recent thrombi are composed of platelets and fibrin with hardly any cells implying that they were built up slowly. That the earlier, now organized thrombi had been mainly of this type can be deduced from the absence of any iron pigment in appropriately stained sections. Some thrombi are covered in parts by no more than a layer of endothelium, indicating that they are very recent. At all levels examined there is absence of any significant atheroma. There is some fat present but there is none of the necrotic atheroma commonly seen in the aortas of elderly people. The medial coat is traversed by enlarged vasa vasorum where it underlay intimal organization, but there is no lesion that can be interpreted as arteritis. There is, in fact, no evidence to indicate what provoked the original thrombosis."

DISCUSSION

Primary arterial thrombosis is a rare lesion and may be defined as thrombosis of an artery without any obvious underlying cause. The condition has been described in the major arteries of the upper and lower extremities, but there are few authenticated reports of the condition affecting the aorta. Learmonth, Blackwood, and Richards[5] recorded 4 cases in young adults in which peripheral arteries were affected and termed the condition "localized arterial thrombosis of indeterminate origin." A similar condition was reported by Leriche[1] and Stricker under the heading of "spontaneous localised monarteritis of indeterminate origin." Boyd et al.[6] reported 6 cases of primary popliteal thrombosis in young healthy men. In all these cases, minute injuries, the result of muscular exertion or abnormally developed fascial bands, were considered to be possible causes.

If the definition of primary arterial thrombosis is accepted as thrombosis occurring in

an artery showing no obvious underlying pathology, then primary thrombosis of the aorta is a rare condition. In the literature there is confusion concerning the meaning of the term primary thrombosis. Welch[7] reported 7 cases of primary aortic thrombosis in a series of 59 cases of abdominal aortic occlusion. From the description it is doubtful whether they were truly primary; all appeared to be secondary to embolism of either the iliac or femoral arteries. Hinckle and Vinson[8] reported a case of "primary thrombosis of the abdominal aorta associated with primary thrombosis of the left pulmonary artery;" the aortic thrombosis developed on an underlying ulcerated atheromatous plaque.

Most pathologists agree that there is often considerable difficulty in distinguishing between thrombosis and embolism. The symptoms too may not help to clarify the issue. In the case reported here, there was no history of rheumatic fever or myocardial insufficiency, and the clinical examination, electrocardiogram and x-ray findings of the heart were normal. It is then most unlikely that the occlusive process was embolic in origin. Serial histological examination of the affected vessels showed no evidence of arteritis or atheroma and there was no evidence to indicate the etiology of the thrombosis.

Summary

A case of primary aortic thrombosis occurring in a man aged 32 years is reported. There was no evidence to indicate what provoked the original thrombosis. The aortic bifurcation was resected and continuity was restored with a polyvinyl alcohol sponge prosthesis.

Acknowledgment

I wish to thank Professor C. V. Harrison for the interpretation of the histologic sections.

Summario in Interlingua

Es reportate un caso de primari thrombose aortic occurrente in un masculo de 32 annos de etate. Esseva trovate nulle indication del causa que provocava le thrombose original. Le bifurcation aortic esseva resecate, e le continuitate esseva restaurate per medio de un prosthese a spongia de alcohol polyvinylic.

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CLINICAL CONFERENCE

Editor: EDGAR V. ALLEN, M.D.
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Long-Term Management of Patients with Coronary Artery Disease

By LAURENCE B. ELLIS, M.D., HERRMAN L. BLUMGART, M.D., DWIGHT E. HARKEN, M.D., HERBERT S. SISE, M.D., AND FREDRICK J. STARE, M.D.

DR. LAURENCE B. ELLIS: Our conference today is on the long-term management of patients with chronic coronary artery disease, with particular emphasis on the more radical methods of therapy. This is intended to be a practical discussion for practicing physicians and our hope is to put into perspective the special methods of treatment that have been advocated, either directly or by implication, as the result of some of the more recent investigations. Anyone who reads medical journals or even any of the printed matter offered by the pharmaceutical houses is bombarded by various special methods of treating coronary disease. One can but wonder whether he may not be neglecting some useful therapeutic device that might benefit the future course of his patients. With the aid of experts in several special fields I shall attempt to separate some of the wheat from the chaff in this important and perplexing problem.

I need not remind you that coronary atherosclerosis occurs to a greater or lesser extent almost universally in human beings and its fatal consequences are so numerous that the disease is now the leading cause of death in the United States; nor need I remind you that it occurs much earlier and in a more severe form in men than in women. There appears to be undoubtedly a constitutional trait predisposing to premature coronary atherosclerosis in certain family stocks. To what extent the physical and emotional stresses and strains of life hasten the development of coronary atherosclerosis has not yet been proved. Most cardiologists however are of the opinion that coronary insufficiency as manifested either by pain or by myocardial failure may be hastened by such stresses.

In the evaluation of any studies concerned with coronary artery disease, one must remember that it is possible to make a diagnosis of this disease in life only after some breakdown in the coronary circulation has occurred, such as a myocardial infarction, the development of angina pectoris, or congestive failure. This makes it almost impossible to carry out controlled studies of the type that one would like to have concerning the value of various therapeutic or diagnostic procedures. Physicians should bear this in mind when they peruse the many articles that are written on this subject and they should also remember that coronary artery disease gives rise to no specific physical signs. The physical signs that do develop in patients with this disease reflect changes in the state of the myocardium. This is true also of the electrocardiogram which, of course, in no way is a direct measure of the state of the coronary circulation, but only an indirect index, reflecting changes in those potentials produced by excitation of the myocardium itself. The same reservations must be made in regard to the value of the ballistocardiogram, only more so. It can-

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not be emphasized too much that the diagnosis of angina pectoris is chiefly made from an evaluation of a carefully taken history as given by the patient, and that physical signs and laboratory tests are only of ancillary importance in helping to support the diagnosis of this subjective symptom indicating coronary insufficiency.

In general, the first principle in the treatment of coronary disease is to adjust the energy budget of the individual so that his heart, with a limited performance capacity, will not be called upon to meet greater demands than it is capable of supplying. Every patient should be individualized because his cardiac reserve is different. The patient's schedule of living should be so arranged that he is not called upon to do more than he can carry out, and a reasonable margin of safety should be provided. Beyond this, however, it is probably not advisable to restrict the activity of patients, and since many of them have virtually a normal cardiac reserve, there is no reason why they should not lead a normal life provided they do not go in for physical or mental excesses. The avoidance of unusually severe activity, of course, should be prescribed but regular exercise within the capacity of the patient is advisable and many patients with coronary disease who have always carried on an active physical life can still remain quite active after convalescence from a nonincapacitating coronary accident. Relatively few patients after a myocardial infarction have to leave their previous occupations. The physician should always keep in front of him the goal of returning the patient to that type of life which is most economically productive and satisfactory to him, so avoiding insofar as possible the psychologic hazard of seriously disrupting a patient's life by forcing him to give up work or to change to a less satisfactory occupation. Psychologic damage may well be as bad as physical strain. Detailed attention to the proper regulation of the patient's life and habits with the aim of giving him a maximum of satisfaction and happiness should be the prime objective of the physician. Since this often involves time-consuming effort it is often neglected, whereas many doctors tend to overemphasize drug treatment in the attempt to control coronary artery disease.

A cardinal objective in the management of coronary artery disease is to remove or reduce the various burdens on the circulation. Although, as said, most people can continue in or return to their previous occupations, nevertheless, they should live at a more gentle pace than that to which they were formerly accustomed. With detailed attention to the regulation of the patient's life; that is, by cutting out the unnecessary and inefficiently performed details of living, and by increasing rest periods during the day, on weekends, and in vacations, his budget of energy can be very markedly conserved. Naturally if he develops symptoms of severe angina or of cardiac insufficiency, his activity will have to be restricted further.

The second burden that should be removed is excess weight. The well-treated cardiac patient is one who is underweight. Other extrinsic burdens on the circulation should be searched for and removed whenever possible such as anemia, minor infections, etc.

There is no clear evidence that there is anything that definitely controls the progress of atherosclerosis in human beings. However, patients with coronary disease cannot wait until some future time when proof of the value of certain therapeutic measures is forthcoming. A proper therapeutic approach at the present time is to institute those therapeutic measures from which there seems a reasonable likelihood that benefit will result but to avoid highly experimental, expensive, or drastic measures that may be seriously disrupting to the person's mode of living and happiness.

We naturally turn first to vasodilating drugs in these patients, particularly those suffering from angina pectoris. There is no question that nitroglycerin is the most effective for the acute relief of individual attacks. There is no agreement as to whether long-acting vasodilators are of specific value in

diminishing the number of attacks of angina pectoris, and certainly there is no evidence that the routine use of such drugs in patients without symptoms is of any value in diminishing the possibility of future coronary accidents. Therefore such drugs should be given only for the relief of symptoms and not as routine measures.

Angina pectoris is notably affected by psychogenic influences. Many drugs as well as other methods of therapy if administered enthusiastically and with conviction will ameliorate the number of attacks in some patients, at least for a time. This undoubtedly explains many of the favorable reports of various methods of therapy and at the same time is a justification for a psychotherapeutic approach to the patients, including the judicious use of relaxant drugs.

What further methods are there by which we might control the advance of atherosclerosis in human beings. First of course we think of control of the diet. I shall ask Dr. Fredrick Stare if he will discuss the practical dietary management of these patients with chronic coronary disease in the light of our present knowledge.

Dr. Stare, there has been recent interest in the administration of sitosterol to patients in the endeavor to block the absorption of cholesterol as well as of other so-called lipotropic substances. Will you also tell us whether there is evidence that sitosterol or the various lipotropic substances are of value and whether we should institute such treatment in our patients?

Dr. Fredrick J. Stare: May I first dispose of the so-called lipotropes and of the various sitosterol preparations. Choline and methione are the common lipotropes. Under certain experimental and chemical conditions they may be limiting factors in fat transport and metabolism, but these conditions have not so far included atherosclerosis or coronary artery disease. I know of no evidence that they have a useful role to play in the treatment or prevention of atherosclerosis or any of its complications.

Sitosterols if taken in suffiicient quantity, and each time food is consumed, will impair the absorption and reabsorption of cholesterol and hence lower the level of serum cholesterol. But the large quantities that must be taken to induce a response, together with the intolerance of many patients to the material—to say nothing of its cost—limit its usefulness appreciably. I do not think the administration of sitosterol preparations is of practical importance in decreasing the level of cholesterol.

Recent nutritional researches suggest a number of specific dietary approaches that may be helpful in the management of patients with coronary artery disease.

First, attention should be given to weight reduction, particularly if the patient is overweight. But even if he is of desirable weight, a loss of as little as 3 to 5 pounds is frequently accompanied by a decrease in serum cholesterol of the order of 10 to 15 per cent. This decrease in cholesterol may not be maintained when calorie equilibrium is re-established, but if not, other dietary therapy may be tried.

Weight reduction is not a complicated matter if its importance is explained and sufficient motivation stirred up and maintained. No single food need be eliminated from the diet. It simply is a matter of eating less. Cutting down, not out—smaller portions, no seconds, common sense—and checking up on oneself by a weekly stand on the bathroom scale. As has been said earlier, "the well-treated patient is one that is underweight."

Second, in addition to advising weight loss, the physician might propose that the patient try a diet in which the total calories derived from fat are reduced to 25 to 30 per cent. Such a diet would entail a reduction of most of the visible saturated fats. This can be accomplished by trimming fat from meat, eating more lean meats and smaller servings, more fish, and consuming less butter, margarine, whole milk, cheese (except cottage), bacon, and egg yolks.

Another dietary regimen that can be tried is one that provides our accustomed 40 to 45 per cent of calories from fat but one in which the fats that are good sources of es-

sential fatty acids are emphasized, so that they might supply about 25 per cent of the fat calories, or 10 per cent of the total calories. In our experience it has been difficult to increase the essential fatty acids any more than this without going to formula diets.

If the patient is acutely sick from one of the complications of atherosclerosis, therapy might include a very low-fat diet—one with 20 per cent or less of the calories coming from fat. Also, for the sick patient a formula-type diet might be tried containing a suitable vegetable oil as the sole source of fat.

The avoidance of excessive fat, particularly in the evening meal, may be desirable from the viewpoint of decreasing the chances of intravascular clotting. It has been established that blood is more likely to clot 2 to 7 hours following a high-fat intake. The explanation for this is as yet unknown but is not thought to be associated with the lipemia that ensues. I think it would be good judgment to advise the coronary patient under treatment, and the postcoronary individual who has completely recovered, to get the bulk of his fat and protein calories at breakfast and midday and have a light supper such as soup, cereal, and a fruit salad.

In the light of all of these developments, the physician has a real opportunity to practice good preventive medicine with regard to our leading cause of death. First, it is his responsibility to reassure the public and to prevent mass hysteria for drastic changes in our diets; and second, to guide his patients, depending on their individual status, along dietary patterns that consider advances in research.

DR. ELLIS: Dr. Stare, will you say something about the practical value of the determination of serum cholesterol or other blood tests?

DR. STARE: The determination of the serum total cholesterol is the most important single blood test I am aware of in relation to this problem. Determination of various serum lipoprotein fractions is of course a part of various research studies but does not have, so far as we know, any advantage in assisting with diagnosis or prognosis. For adult mal s I think we can say that a serum total chol - terol much above 225 to 235 mg. per cent s getting a little higher than we should like o see it—something below 210 to 215 is pref - able. There is no question that corona y artery disease is more prevalent in individ - als with an elevated serum total cholester . This is particularly true in males 50 yea s or younger.

DR. ELLIS: Recently there has develop d interest in the long-term use of anticoagulan s in patients suffering from coronary arte y disease. This is obviously a very importa t problem because every doctor will want to know whether he should make the extra effo t involved in instituting this difficult and e - pensive method of treatment that is not wit - out some hazard. I shall ask Dr. Herbert Sise, who has made a particular study of anticoagulants, to give his opinion of the evidence concerning their routine use in patients with chronic coronary disease.

DR. HERBERT S. SISE: Long-term use of anticoagulants is still in the experimental stage. The early results are sufficiently promising to consider that this method of treatment may have considerable usefulness in selected individuals. As you have pointed out earlier, the evaluation of the effectiveness of any kind of treatment of this disease is most difficult. It is not possible to rely on symptoms alone. Consequently, to date the effects of long-term anticoagulants have been assessed by the mortality rates in treated groups versus untreated groups. This method requires a large series of patients, a strict control group, and a sufficient length of time for the mortality rates in either groups to be significantly great. To date, several studies have been reported. The mortality rates in the treated groups have varied from 7 per cent to 12 per cent and in the untreated groups from 28 per cent to 33 per cent, an improvement that is quite impressive and certainly a better result than in the short term treatment of the acute phase of a myocardial infarction. These are gross mortality figures, however, and the control groups are

or the most part not strictly comparable to ie treated ones. The results have been sufciently uniform, however, to stimulate more xtensive and better controlled studies in his country and elsewhere. I am led to beeve that these studies, so far, tend to conrm the earlier and less well controlled reorts. The long-term use of anticoagulants onsequently offers a very encouraging avenue f treatment. It is burdensome and a proedure not without danger, but is not extraordinarily expensive and the cost probably ould be made quite reasonable if large groups vere followed. At the present time the rouine use of anticoagulants is not justified. When employed it should be only with full knowledge of the effects and properties of the drugs.

DR. ELLIS: By what tests should these patients be followed?

DR. SISE: Dr. Ellis has asked me a loaded question because he knows I have been interested in which blood clotting factors are important in the evolution of hemorrhage or of thrombosis during treatment with anticoagulants. Originally in our group of patients on long-term anticoagulant we were puzzled, as others have been, by the occasional individual who will experience hemorrhage at a prothrombin time that is within the therapeutic range or even below it. We were subsequently able to show that fluctuations in the level of the specific clotting factor called prothrombin could take place without a change in the prothrombin time. We now measure both the specific prothrombin value by Owren's 1 stage method as well as the ordinary prothrombin time by Quick's method. By keeping the prothrombin value between prescribed levels the incidence of hemorrhage in our group of treated patients has dropped from a rather high level of nearly 30 per cent down to the vicinity of 5 per cent without any increase in the incidence of thrombosis during treatment.

If measurement of the specific prothrombin value is not available, the 1-stage Quick procedure as performed widely throughout the country gives a sufficiently good guide to estimate correctly the dose in 80 per cent of cases, but bleeding and ineffective treatment in some will be experienced.

DR. ELLIS: There are 2 other types of radical therapy in current use for patients with severe angina pectoris. We are in general agreement that such treatment should be reserved for patients in whom the pain cannot be sufficiently controlled by the methods described above to permit them to live an economically satisfactory life, and even more for the patient who is having angina decubitus to such an extent that his very resting existence is miserable and whose condition is undoubtedly worsened by the continued anxiety of the anticipation of recurring pain and the fatigue resulting from lack of rest. Dr. Herrman Blumgart has made a particular study of the effect of reduction of thyroid activity in the treatment of angina pectoris and I shall ask him to tell us what his present feeling is in regard to the application of this therapy and to what type of patients it should be given; what results may be expected; and what the dangers and difficulties are, if any.

DR. HERRMAN L. BLUMGART: A decade of experience in the use of radioiodine in the treatment of intractable angina pectoris is now available. I shall confine my remarks today to its employment in the treatment of such patients and shall not discuss patients with intractable congestive failure. The purpose of this treatment is to reduce the circulatory requirements so that they may be within the limits of the cardiac reserve. More than 100 patients have been treated in our clinic and the evaluation of results in over 700 patients with angina pectoris is available from 49 other clinics.

The following conclusions may be stated. Hypothyroidism can be induced regularly in patients with intractable angina pectoris without risk or toxic effects. All such patients receive small doses of 6 to 30 mg. of thyroid daily to maintain them at the lowest level of metabolism consistent with comfort. Undue elevation of serum cholesterol is reduced thereby and in some patients may be only moderately increased. In most patients

with rheumatic heart disease who have died after 1 to 11 years in the hypometabolic state, little or no coronary atherosclerosis has been noted; in some, there has been no more than seen in patients not treated with I^{131}.

Approximately 3 quarters of all patients with intractable severe angina pectoris have shown worthwhile improvement; in one half of this group, the improvement has been great and many have been restored to an active gainful life. In the other half the improvement while not as marked has been considerable.

Patients should be selected who have not responded to the usual medical measures for at least 6 months, whose clinical course is not markedly progressive and who will be reasonably cooperative. Of all patients who have angina pectoris, this group comprises less than 5 per cent of the total.

Six weeks to 6 months are required to produce hypometabolism. Consequently this method of therapy should not be invoked in terminal cases.

If radioiodine is not available, the thiourea derivatives may be used. They do not produce hypothyroidism with regularity and high dosage may be necessary. Moreover, drug reactions are not uncommon.

We believe that radioiodine therapy is the treatment of choice in these patients, restoring these incapacitated patients to comfortable and worthwhile existence without the inevitable risks of surgery.

DR. ELLIS: An alternative method of treatment with patients with severe angina pectoris has been some type of surgery, on the heart itself or the nerve supply to it. Operations designed to interrupt nerve pathways have been carried out for a number of years. I will ask Dr. Dwight Harken first to give his opinion as to the value of such operations today.

DR. DWIGHT E. HARKEN: Many operations have been designed to interrupt the nerve pathways to relieve the pain of angina pectoris. We abandoned this type of therapy in 1952. On the whole, pain was alleviated and the fear of angina, itself capable of precipitating attacks, was abolished. Rarely, excruciating pain from trauma to the brachial plexus occurred.

Denervation has been largely abandoned because equally safe operations have been devised, which are just as effective in pain relief, and, in addition, provide at least a theoretical opportunity for increase in the blood supply to the myocardium.

DR. ELLIS: For a number of years now there have been proposed various operations that are designed to improve the vascular supply to the heart. Perhaps Dr. Harken will discuss briefly what some of these operations are and what they are designed to do and the particular type of operation that he himself favors.

DR. HARKEN: Dr. Ellis, many surgical technics have been worked out in the animal laboratory that protect against coronary occlusion. Such procedures have relieved angina pectoris in many patients. The question is which one is most likely to bring a new blood supply to the heart of the human patient with coronary disease and which can be performed with the greatest safety to the patient.

A number of operations have been devised that consist of introducing some type of powder into the pericardium to produce adhesions coupled with certain other accessory procedures. The first of these was devised by Beck. In addition there have been operations in which ligation of the coronary vein and pericoronary neurectomy have been performed, Vineberg's procedure of implanting the left mammary artery into the myocardium, and more recently Beck's operation in which a shunt was made between the aorta and coronary sinus in an attempt to perfuse the coronary bed in a reversed direction.

So, the list could go on with mention of any number of control experiments in which the anterior descending coronary artery was ligated to find that approximately 70 or 75 per cent of animals succumb. Conversely, after any of these and other "protective

maneuvers" the mortality after anterior descending coronary artery ligation fell to 5 per cent. It is rather interesting that these operations have uniformly protected. Such experience has thus been transferred to the human being. Again, with surprising regularity the human subjects have been relieved of pain almost immediately, long before new vessels could have grown in. Some other factor represents a common denominator in the relief and protective effect of these operations. This common denominator may well be the opening of intercoronary communications. This is important and probably related to the considerable relief of pain in people with angina. Whatever the common denominator, the fact remains that relief of pain in patients with angina has been possible and protection of animals has been uniform. The only difficulty has been that these various procedures have carried a substantial mortality rate and have not, therefore been popular.

Moreover, Burchell has shown that none of these procedures designed to promote "a vascular blood supply to the myocardium" produces significant arterialization in terms of vessels that will take the Schlesinger mass. The epicardium remains a barrier.

With this basic knowledge and philosophy, more than 10 years ago we addressed ourselves to the problem of taking off the epicardium. We tried to remove the epicardium surgically and with various chemicals. After a host of experiments we finally found that the least traumatic, paradoxically enough, was 95 per cent phenol to slough off the epicardium. After de-epicardialization with phenol, talc was instilled and the lung brought to the myocardium. Blood vessels that would take the Schlesinger mass were subsequently found to run from the adhesions into the myocardium.

We thought that this operation could be performed so quickly that there would be little opportunity for tachycardia and drop in blood pressure, and therefore little opportunity for further coronary occlusion. I think this is extremely important in these patients, for a fair number of people with angina decubitus who do not respond to medical treatment are going to die before, during, or after surgery. At any rate, this simple operation of phenol de-epicardialization, poudrage, and pneumonopexy can be performed in 12 to 20 minutes. It goes quickly and the patients are rather consistently relieved of pain. Whether they have a new blood supply, as suggested in animals, I cannot say but it would appear that patients so operated upon may be exceeding their anticipated life span. At least they are living longer than the denervated patients did years ago, and the patients have been selected on the same basis.

In short, we offer the patient an operation that *may* increase his blood supply and will usually relieve his pain. Carry in mind a low surgical risk for this operation. Thirty odd patients have had this operation, with 3 surgical deaths. Whenever the medical problem is great enough to assume this risk to relieve pain, the basis for recommending surgery is firm. You have an extra dividend in the "hope that you may increase the blood supply."

DR. ELLIS: Dr. Harken, we have been hearing about ligation of internal mammary arteries for the possible relief of pain. What do you think of this?

DR. HARKEN: Dr. Ellis, I was afraid you would ask that. I cannot give you a very good answer. Whenever an operation is advanced for the treatment of angina, one must start out with the assumption that the patients are relieved if the authors say so. The anatomist Von Hollerin suggested that occlusion of the internal mammary arteries below the pericardiophrenic branches might increase the volume of blood flow through the pericardiophrenic vessels and thence to the heart. Fieschi of Italy and his colleagues interrupted the mammary arteries bilaterally in the second interspaces. We have been conducting experiments that we hope will show us how such a mechanism may operate.

Also, because of the remarkable simplicity of the operation, we have done it in 8 patients. In all the relief of pain was spectacular. The period of observation has been too short for us to make further comment.*

In leaving this aspect of this subject, we really fade out on a feeble chord because we know little about the mechanism that may be back of the relief of pain by interruption of the mammary arteries, if indeed it exists on a permanent basis at all. It could be that there are sympathetic fibers traveling over the mammary arteries that are interrupted, and it might be that it makes a difference whether the veins are interrupted as well. Many surgeons are carrying out this procedure under general anesthesia. We view with some question any operation that is associated with a general anesthetic because these patients are apt to have relief of pain on the nonspecific "common denominator basis" mentioned previously. Our operations have been conducted under local anesthesia. It is a safe, almost office procedure. If you have angina yourself and press firmly on your precordium, you will find that some relief of pain is produced thereby. It is entirely possible that this transverse incision is something like the blocking of reference areas of referred pain. The mechanism is not clear, the facts are not well established, but the present experience is indeed exciting.

DR. ELLIS: We have presented to you in brief form a schema for the long-term management of coronary artery disease. We have had the opinions of several experts as to the current status of certain of the so-called radical methods of therapy. We have not attempted to assess the *relative* value of one such treatment against another. Most methods must still be considered experimental, and their ultimate value will be established in the course of time by further studies.

*Thirty-five patients have now had internal mammary artery ligation. More than a third have enjoyed complete relief and there has been worthwhile palliation in almost three fourths of the group. The remainder have been total failures or have never had full return of symptoms. This seems a simple but valuable therapeutic adjunct. The associated denervation probably accounts for the relief of pain.

Jennings, R. B., Crout, J. R., and Smetters, G. W.: Studies on Distribution and Localization of Potassium in Early Myocardial Ischemic Injury. Arch. Path. **63**: 586 (June), 1957.

In a previous study the authors demonstrated that complete, or almost complete, necrosis of the posterior papillary muscles could be produced in dogs by high ligation of the left circumflex coronary artery and that comparable samples of this region are easily obtainable for both chemical and histopathologic study. Chemical analyses of experimentally produced infarcts showed a 10 per cent loss of potassium in the first 60 to 90 minutes, and a more rapid disappearance during the subsequent 12 hours, when the level had fallen nearly to that contained in extracellular fluid. Histochemical studies using a cobaltnitrite method of precipitation confirmed these results by demonstrating little or no potassium in the fibers at the end of 12 hours. The data suggest that the potassium ion leaves the irreversibly injured fibers at a slow rate during the first 2 hours after injury. Whether this is due to failure of energy-producing mechanisms involved in maintaining the normally high intracellular gradient of potassium or to delayed release of potassium containing proteins is not known.

MAXWELL

CLINICAL PROGRESS

Penetrating Wounds of the Heart and Aorta

By Loren F. Parmley, Lt. Col., MC, Thomas W. Mattingly, Brig. Gen., MC, and William C. Manion, M.D.

Part I.

Penetrating Wounds of the Heart

MANY centuries ago it was believed that a heart wound was inevitably lethal. This dictum stood unchallenged until the eighteenth century, when it was first recognized that an individual might suffer a heart wound and continue to live without evidence of serious injury. For the detailed historical evolution of the treatment of traumatic heart disease the reader is referred to Sir Charles Ballance's outstanding Bradshaw Lecture[1] and Beck's more recent[2] amplification. The first successful pericardiocentesis for hemopericardium was performed in 1829,[1] but it was 39 years later before Fischer's[3] classic work on heart wounds was published. He based his observations on 452 cases in which the mortality was 84 per cent. Suture of cardiac wounds was suggested by Roberts[4] in 1881, and a year later it was performed experimentally in animals by Block.[5] Cappelen[6] was the first to attempt suture of a wound of the human heart; his patient died, but the following year Rehn's attempt was successful. By 1909 Peck[8] had collected 160 cases of heart wounds treated surgically, and since then surgical therapy in such cases has become relatively commonplace.

Table 1 is an analysis of our postmortem series of missile and stab wounds of the heart and aorta. The site and the cause of the penetrating injury have been listed in relation to death and length of survival. Although 72, or 15.7 per cent, of the patients survived the immediate effect of injury, the significant figure is the 12.2 per cent who survived long enough to receive adequate medical care.

It is the purpose of this paper to review the incidence, mortality, and morbidity of penetrating cardiac wounds, emphasizing the important clinical features and complications of such injury. In this way the medical management of those who initially survive injury might be improved. Nonpenetrating traumatic lesions of the heart and aorta will be reported subsequently.

The incidence of cardiac injury in penetrating thoraco-abdominal wounds and the ultimate survival rate after penetrating cardiac wounds have not been clearly established. It has been estimated that 30 per cent of penetrating wounds in time of war are thoraco-abdominal,[9] but the percentage in which cardiac injury is a factor can be only roughly surmised. In the experience of a group in World War II, as reported by Samson,[10] the heart was involved in 3.3 per cent of 2,267 thoraco-abdominal wounds caused primarily by shell fragments. Elkin,[11] in reviewing his cases of thoracic wounds, mostly stab wounds, states that 2 per cent involved the heart. In a series of 2,811 chest wounds treated at the Tokyo Army Hospital, Valle[12] reported involvement of mediastinal structures in 4.2 per cent. From these reports it may be estimated that 2 to 3 per cent of all penetrating thoracic wounds involve the heart.

There have been many comprehensive reports of penetrating cardiac wounds with survival. In the more recent ones[13-19] a consistent increase in rate of survival has been noted, up to 88.9 per cent in Elkin's

From Department of Medicine, Walter Reed Army Hospital, and Armed Forces Institute of Pathology, Washington, D. C.

TABLE 1.—*Survival Times in 456 Necropsy Cases of Penetrating Wounds of the Heart and Aorta*

Type of injury Site	DOA or immediate	30 min.	30 min. 1 hr.	1 hr. 6 hrs.	6 hrs. 24 hrs.	24 hrs. 3 days	3 days 7 days	7 days	Total
Missile									
Heart	225	2	1	2	7	2	3	11	28
Multiple chamber and/or aorta	31	2	–	–	2	1	–	—	5
Aorta	37	–	–	–	2	–	–	7	9
Stab									
Heart	55	5	4	5	2	3	1	4	24
Multiple chamber and/or aorta	20	1	–	1	–	–	–	–	2
Aorta	16	–	1	1	–	–	–	2	4
Total	384	10	6	9	13	6	4	24	72

72 or 15.7% survived for variable periods.
58 or 12.7% survived over 1 hour and long enough to reach medical attention.

series of stab wounds[15] and 64.9 per cent in Samson's series of missile wounds.[10]

Causes and Types of Penetrating Wounds

Many objects may produce penetrating wounds of the heart. Decker's[20] analysis of 100 foreign bodies retained in the heart gives a good idea of their variety, from toothpicks to dental plates, and points up the fact that foreign bodies, especially those within the chest, can migrate and penetrate the heart in the course of their wanderings. This is particularly true of esophageal or bronchial foreign bodies that erode through these structures and enter the myocardium.[21] Foreign bodies may be carried to the heart via vascular channels after having penetrated a vein or artery. Occasional reports in the literature tell of penetrating wounds of bizarre origin, such as the one caused by the spine of the sting ray.[22]

Most of the wounds in our cases were produced by missiles, the largest number by shell fragments, with gunshot wounds next in frequency. However, in a few cases the injury was caused by secondary missiles, i.e., bone, various debris (in one instance "dog tags" and in another a 1-cent piece) which became missiles because of blast effects or because they were struck by high velocity missiles. Stab wounds were less frequent in our series but are the most common type of penetrating wound in civilian life.

A penetrating cardiac wound may only lacerate the pericardium or myocardium; it may penetrate the chambers of the heart, or it may perforate the heart through a single or through multiple chambers and at times the septa. The distribution of these injuries in our series revealed no particular predilection for any chamber, except that the incidence of wounds of the left atrium was low, no doubt a reflection of its dorsal anatomic position. One would not expect survival after some of these cardiac wounds, particularly perforating wounds involving multiple chambers, vessels, or both. Certainly those that almost destroy the heart, as suicide gunshot wounds frequently do, are invariably fatal. Nevertheless, a surprising number of patients with perforating missile and stab wounds of the heart survive, some with astonishingly few cardiovascular symptoms, so few, in fact, that the cardiac wound may be overlooked. Patients with lacerating and penetrating wounds have, in general, a better prognosis. Retention of a penetrating missile always indicates that the missile was of low velocity, usually a shell fragment or a secondary missile. Frequently its velocity is so spent that the missile may be retained in, or merely impinged upon, the pericardium or epicardium. Patients with missile wounds of this type often survive and make up the major number of those reported as surviving.

Although not a penetrating wound of the eart in the strict sense, considerable damage ıay be caused by a high velocity missile pass-ıg adjacent to the heart. Such a primary ıissile creates secondary missiles from the issue through which it passes. Recognition ·f this effect is of great importance in the linical evaluation of penetrating wounds, ›articularly those of the heart and great ves-·els. In 1 of our cases, rupture of the right ·entricle, without pericardial laceration but vith resultant cardiac tamponade, occurred vhen a high velocity missile passed near the ıeart.

Clinical Aspects

Every penetrating injury of the thorax or abdomen should be suspected of involving important cardiovascular structures even though cardiac signs or symptoms are absent. In our series there are several instances in which an extremity was the site of entrance of a missile that subsequently penetrated the heart.

The immediate catastrophic events that may follow penetrating cardiac injuries are hemorrhage and cardiac tamponade. It was not too many years ago that infection was the primary problem, but proper prophylactic measures, chiefly antibiotic therapy, have diminished this threat. In the presence of cardiac tamponade, pericardiocentesis has been recommended as the main therapeutic procedure. However, pericardiocentesis is not without danger and should be performed only when there is evidence of tamponade and not of hemopericardium alone. Emphasis has been placed[15, 19, 23] on the conservative approach in the initial treatment of penetrating cardiac wounds, with almost complete reliance on paracentesis in the event of tamponade. However, there are definite accepted criteria[24] for immediate operation: (1) tamponade unrelieved by pericardiocentesis because of clots, (2) rapid recurrence of tamponade, and (3) continuing hemorrhage externally or into the thoracic or abdominal cavity. Others[16–18] believe that surgical intervention should be immediate, irrespective of the circumstances. Impressive statistics have been presented by both groups in support of their contentions. The surgical aspects of the treatment of penetrating injuries of the heart and pericardium, whether missile or stab wounds, have been well presented by those who have had wide experience in this field of traumatic injury, and the reader is referred to Beck,[2] Harken et al.[25-27] and others.[17, 18, 28] In the future the newly developed technics of cardiotomy utilizing extracorporeal circulation and asystole will probably alter the surgical approach to many of these lesions.

TABLE 2.—*Cause of Death in 121 Cases of Stab Wound of the Heart and Aorta*

	Heart	Aorta
Hemopericardium	32	3
Hemopericardium with large clots	10	—
Hemothorax or other internal or external hemorrhage	30	15
Combination hemopericardium and hemothorax	13	2
Infection	4	—
Post operative surgical complications	3	—
Unknown	9	—
Total	101	20

Most of the reports on the management of penetrating wounds of the heart have been based on experience with stab wounds; therefore, in the analysis of our postmortem material we have given particular attention to cases of stab wounds in an effort to determine the cause of death. There were 121 such cases (table 2) and in 57 per cent of these, death was a result of hemorrhage or tamponade with large clots that probably would have prevented adequate paracentesis. Thus, in over half the total group the accepted criteria would have dictated surgical treatment, and recurrent tamponade would probably have called for surgical measures in others. There are no statistical data to indicate the number of individuals with similar wounds who survived; also the number that no kind of treatment could have saved is probably large. Nevertheless, the analysis indicates that death in most cases of stab wounds of the heart is the

TABLE 3.—*Tabulation of Surviving Patients with Missile Foreign Body Retained in the Myocardium*

Site of foreign body	Number of patients
Right ventricle	3*
Left ventricle	4
Right atrium	3
Left atrium	0
I. V. septum	3
Total	13

* One patient with foreign body perforation left ventricle, interventricular septum, and lodgment right ventricle.

result of a complication amenable to surgical treatment.

Under most circumstances a hospital geared to the immediate surgical treatment of penetrating heart wounds is not available, and the management must be conservative, including such measures as pericardiocentesis, intravenous infusions,[29, 30] prevention of infection, and other supportive treatment until surgical facilities are available and the need for operation is established. A predetermined opinion about surgical or conservative therapy is dangerous. The management of each case must be formulated individually.

Retained Foreign Bodies

The complications and sequelae of penetrating cardiac lesions are numerous, particularly when the foreign body is retained. Nevertheless, many patients carry missiles within the myocardium without apparent difficulty. We have had the opportunity to observe 13 patients (table 3) with retained intramyocardial shell fragments in various locations, and the majority of these patients were, and probably will remain, asymptomatic. However, there are complications that require careful consideration and these are summarized in table 4.

Numerous cases are on record in which foreign bodies have been retained within the heart for many years, in some instances 40 or 50,[31, 32] without ill effects. Hoffman[33] in 1920 collected 50 cases of asymptomatic foreign bodies from the literature. Since then, Swearingen,[34] Deeker,[20] and many

TABLE 4.—*Summary of Sequelae of Penetrating Wounds of the Heart*

1. Embolism
   a. Foreign body
   b. Thrombus (Septic / Sterile)
2. Bacterial endocarditis
3. Recurrent pericarditis, hemopericardium
4. Pericardial abscess or purulent pericarditis
5. Myocardial injury with or without production of structural defects, aneurysm, septal defects, etc.
6. Coronary vessel injury with or without myocardial infarction
   a. Arteriovenous fistula
7. Rhythm or conduction defects
8. Valvular injury

others[26, 36-37] have reported individual cases or series of cases of this nature that have multiplied Hoffman's figure many times.

A patient in our series, who died of cirrhosis, was found to have a shell fragment, 4 mm. in diameter, embedded in the myocardium of the interventricular septum (fig. 1). He had been wounded 8 years previously, but in the absence of cardiovascular symptoms a myocardial foreign body had not been suspected. Only fibrous and well contracted scar tissue (fig. 2) was seen at the site of the foreign body and tract of passage of the missile. In general, when studies of the myocardium surrounding the foreign body have been made or direct visualization has been possible at operation, similar fibrous encapsulation has been observed. Occasionally calcification[38] has been noted, but more often a small cystic area immediately surrounds the foreign body.

Despite these reports, when such a foreign body is found today, it will seldom be allowed to remain undisturbed. The possible serious consequences of continued retention will be emphasized and too little thought may be given to equally serious possibilities incident to removal. Criteria for the removal of asymptomatic foreign bodies depend in large part on the size, shape, and location of the fragment. As Harken[25] has pointed out, a foreign body less than 1 by 1 cm.

should not be extracted as a prophylactic measure unless there are other indications for its removal. Should it be within the endocardium or impinge upon the pericardium or epicardium, the wisdom of removal must be questioned seriously in view of the complications that so frequently accompany a foreign body embedded at these sites. As emphasized by Swan et al.[28] angiocardiography often will define the location of the fragment, and this technic has been used successfully in patients of our series (figs. 3 and 4). It is well to remember that a fragment seen on x-ray examination often cannot be located on direct palpation, even though it seemed to be in a readily accessible location. Figures 5*a* and *b* are roentgenograms of the chest from a case of this type. The elusiveness of these retained foreign bodies and the damage that might occur during their removal should be restraining factors in a decision on surgical removal. The fragment should be removed if it is sharp or its shape favors migration.

The following case underlines the need for a cautious approach to a foreign body in the myocardium and of a proper evaluation of symptoms that could be interpreted as indications for removal.

Case 1. AFIP Acc. 151350: This 24-year-old soldier was wounded in action by a mortar shell fragment, which left a sucking wound of the right anterior chest. Roentgenograms revealed a metallic foreign body that appeared to be in the right ventricle. The treatment included initial care of the wound and repeated aspirations for hemothorax. An electrocardiogram revealed only nonspecific changes in the S-T and T waves. The patient complained of intermittent substernal pain with radiation to the left scapular region. During these episodes he exhibited anxiety. His condition improved, although the chest pain recurred intermittently. An exploratory pericardiotomy was performed. The foreign body was palpated in the myocardium of the right ventricle on the phrenic surface in the region of the interventricular septum, but it was not removed because the danger was considered too great. Postoperative recovery was rapid. Intermittent chest pain associated with psychoneurotic symptoms persisted. Cardiac examination revealed no abnormalities and the electrocardiogram was normal. It was decided that removal of the foreign body was indicated because of the psychoneurosis and possible anginal syndrome. The operation was undertaken but was terminated by copious hemorrhage from the right ventricle. The postoperative course was stormy,

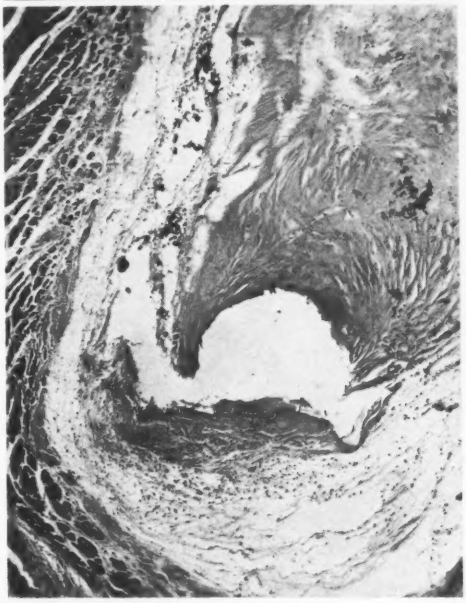

FIG. 1 *Top.* (AFIP 611572) Dissection of the heart demonstrating the scar of the wall of the left ventricle through which a shell fragment passed before becoming embedded in the left ventricular aspect of the interventricular septum.

FIG. 2 *Bottom.* (AFIP 611572) Section of the myocardium surrounding the area where the shell fragment was retained for 8 years demonstrating the fibrous encapsulation that occurred.

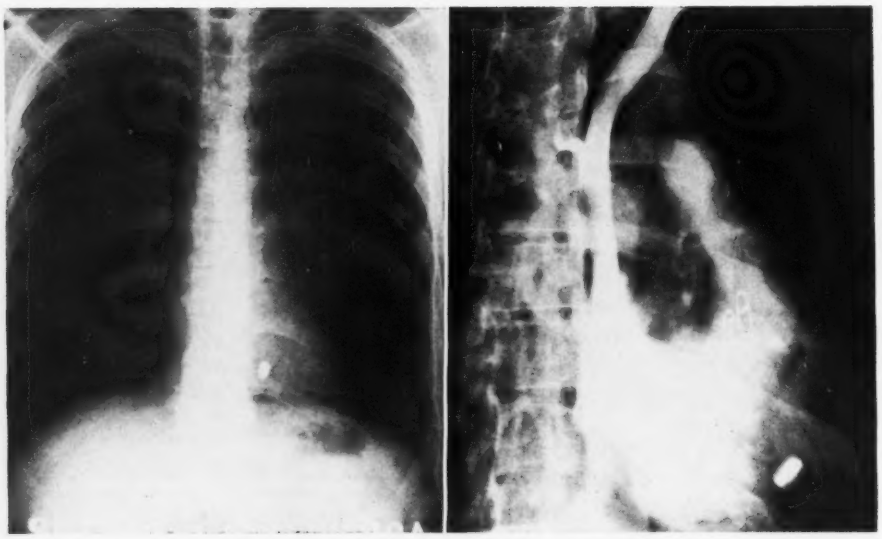

FIG. 3 *Left.* PA roentgoenogram of the chest of a 27-year-old man who incurred a ricochet shell fragment wound of the right posterior lower thorax, demonstrating the missle in the myocardium; the exact location was not determined. Patient was asymptomatic. *Right.* Venous angiocardiogram performed by Dr. George P. Robb with right anterior oblique projection, demonstrating that the retained shell fragment was not in the right ventricle but probably in the interventricular septum. Subsequent angiocardiographic study confirmed this impression. Wire sutures are result of exploratory thoracotomy.

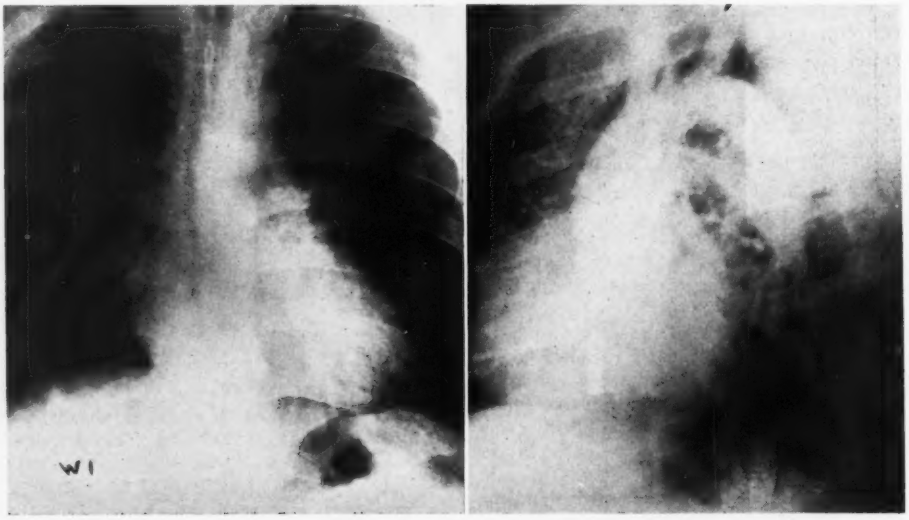

FIG. 4. (*a* and *b*). Postero-anterior chest roentgenogram of a 29-year-old man who was wounded in the right anterior chest by a rifle bullet. Its exact location was undetermined until venous angiocardiogram, performed in the severe left oblique projection by Dr. George P. Robb, demonstrated it to be embedded in the interventricular septum. Surgical removal was not indicated.

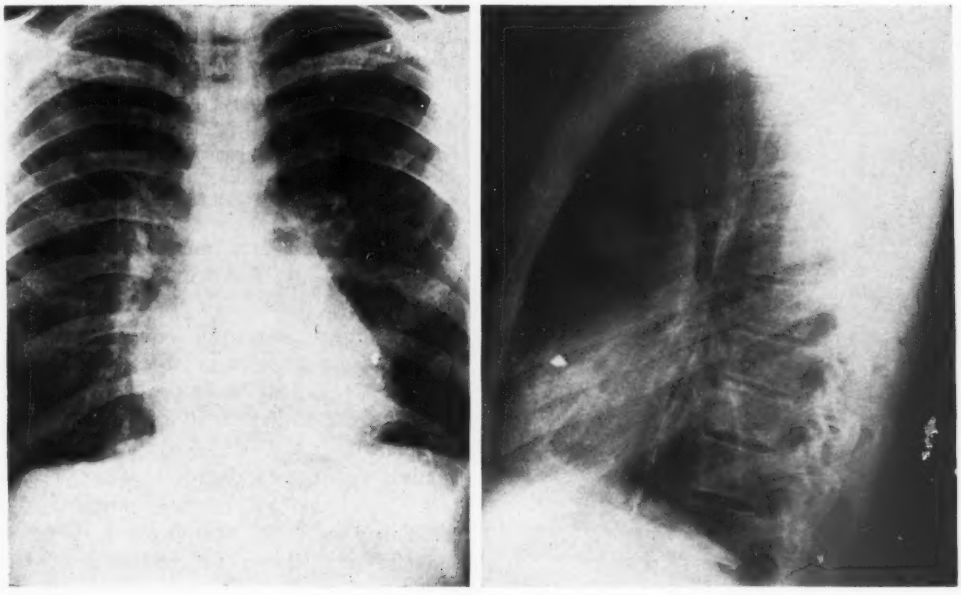

FIG. 5. Postero-anterior and lateral chest roentgenograms after thoracotomy, demonstrating a retained shell fragment in the anterolateral aspect of the left ventricle. This fragment was believed to be accessible, but could not be found at operation.

with frequent bouts of pulmonary edema, and the patient died during such an episode. At autopsy the metallic foreign body, 8 by 5 mm., was found embedded in the right lateral interventricular septum. A hemorrhagic tract, the result of the surgical exploration, led from the apex to the foreign body (fig. 6). A significant compromise of the circulation could not be demonstrated by injection of the coronary artery with radiopaque material.

Comment. The site of the foreign body was such that the wisdom of surgical removal might be questioned. The decision to remove the foreign body in the myocardium when other heart disease was absent was influenced by psychogenic factors arising from the patient's knowledge that he harbored a foreign body. Surgical intervention cannot be regarded as a treatment for psychoneurosis, even one aggravated by the patient's awareness of an intramyocardial foreign body.

FIG. 6. Case 1. Longitudinal cross section of the heart, showing the shell fragment (*arrow*) embedded in the interventricular septum and the extensive hemorrhagic tract incident to the surgical attempt to remove the fragment.

Coronary Artery Injury

The anginal syndrome incident to a foreign body in the myocardium is rare; more often it has been reported as a sequel to nonpene-

trating injuries of the chest with myocardial contusion. Laceration of a coronary artery may result in myocardial infarction, and this occurred in 2 necropsied cases, one due to a penetrating missile, the other to a stab wound. In a third case, thrombosis of the left coronary artery with myocardial infarction was caused by a high velocity missile that passed adjacent to the heart, producing severe contusion of the left ventricular myocardium with coronary thrombosis secondary to hemorrhage and necrosis in the media of the coronary vessel.

Unless injury to a major coronary vessel has occurred,[39] or there has been coexistent contusive injury with or without coronary artery injury as with high velocity missiles, or the missile is adjacent to a coronary vessel,[40] the possibility of true angina pectoris is remote. Referred pain to the left shoulder or neck, simulating angina pectoris, may occur when the foreign body lodges in the diaphragmatic surface of the heart.[41]

Pericardial Injury

Pericardial laceration almost always accompanies penetrating cardiac injury, although it may occur in the absence of myocardial involvement. It is of greatest importance when associated with a lesion that produces hemopericardium, for if the laceration is small, it favors the development of cardiac tamponade when bleeding persists. A larger laceration permits free egress of blood to the thoracic or abdominal cavity. Usually cardiac tamponade or persistent hemorrhage becomes manifest soon after injury, but it may occur days later, particularly if a foreign body is retained within the pericardium. The effects of this complication are demonstrated by the following case.

Case 2. AFIP Acc. 141641: A 37-year-old soldier incurred a sucking wound of the left upper anterior chest from a shell fragment. Exploratory thoracotomy did not reveal the missile, but x-ray examination thereafter demonstrated hemopericardium and a large metallic foreign body that was believed to be in the heart. The postoperative course was uneventful; there was no evidence of tamponade, and the patient soon became asymptomatic. Eleven days later, while being evacuated by air, he suddenly became cyanotic, his pulse imperceptible, and coma developed. Within 20 minutes he was dead. At postmortem the pericardial sac was greatly distended, but nothing was seen that could be identified as a pericardial laceration. However, within the pericardial sac a nosefuse fragment, 3.5 cm. in diameter, was found along with hemorrhage and clot amounting to 700 ml. of blood.

Penetrating heart wounds, usually stab wounds, may also result in hemopneumopericardium, but rarely is it of serious consequence unless associated with laceration of the esophagus or other important mediastinal structure. In the absence of tamponade, treatment of the hemopneumopericardium is conservative. A rarer sequela of penetrating wounds with hemopericardium is the development of constrictive pericarditis.[42] The possibility of this complication does not indicate a need for surgical treatment in every instance of hemopericardium resulting from trauma, for the more severe ones may be treated by pericardiocentesis and the others resolve spontaneously.

A frequent complication of missile wounds is recurrent pericarditis with effusion, which develops when the foreign body impinges upon the parietal or visceral pericardium. The frequency of this complication is such that the belief that a foreign body is in this location is sufficient reason for prophylactic surgical removal.

Less frequent but often fatal complications are myocardial abscess, suppurative pericarditis, and pericardial abscess, particularly in those instances in which the responsible organism is resistant to antibiotics. Shell fragments, usually those of low velocity and with jagged edges, are notorious for carrying foreign material, such as clothing, into the wound. The following case, the surgical features of which were reported in some detail by Robertson,[43] is particularly interesting because of the development of a pericardial abscess.

Case 3. WRAH Reg. No. 23101: This 20-year-old man was hit by a machine gun bullet that ricocheted off a stone wall and inflicted a sucking wound in the first interspace on the right side just

lateral to the sternum. X-ray of the chest showed right hemopneumothorax and a small foreign body at the site of the wound of entrance. At thoracotomy a large laceration in the superior vena cava at its junction with the right atrium was repaired, but the bullet was not found. Pericardial effusion complicated the postoperative course and was treated by aspiration. Roentgenograms of the pelvis revealed a bullet just anterior to the lower border of the fifth lumbar vertebra. A venogram demonstrated that a bullet was in the left iliac vein and it was removed surgically. The bullet was thought to have migrated by gravity from the right atrium through the inferior vena cava to the iliac vein. The patient complained of chest pain and dyspnea and was transferred to the Walter Reed Army Hospital. Fluoroscopy revealed marked enlargement in the region of the left ventricle with diminished pulsations in this region. An electrocardiogram showed changes compatible with pericarditis. In angiocardiograms the left ventricle appeared to be of normal size, but a large mass was contiguous with its left border (fig. 7). The mass was believed to be a hematoma, since there was no significant evidence of sepsis, but on thoracotomy a piece of wool fabric and 200 ml. of pus were removed from the pericardial sac. The postoperative course was uneventful.

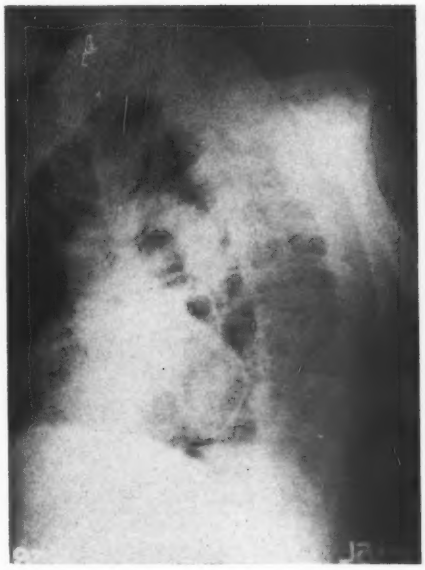

FIG. 7. Venous angiocardiogram, case 3; the pericardium and the abscess it contains are clearly demarcated by the opacified left ventricle.

Embolic Complications

The preceding case introduces another interesting sequel of penetrating heart wounds: embolization. The embolus may be the foreign body itself or a thrombus, either sterile or septic. Embolization may be from any of the great vessels to the heart, or from the heart to any one of the great vessels. The preceding case demonstrates retrograde embolization from the right atrium to a major systemic vein. A similar case has been reported by Grandgérard.[44] These cases represent the phenomenon of gravity rather than true embolization. Davey and Parker[45] reported an example of missile embolization from the left innominate vein to the right atrium to the right iliac vein. Missile emboli to the heart from the vena cava,[46] the femoral vein,[47] the internal jugular vein,[48] and many other sites have been recorded. In the cases reported by Fry[49] and Straus[50] the bullet pursued a course from a systemic vein to a pulmonary artery. Collins[51] has recently summarized 9 cases of embolization of retained missiles to one of the pulmonary arteries. Harken and Williams[26] and others[52, 53] have reported missile embolization from the left side of the heart to systemic arterial vessels. Another case in our series demonstrated embolization of a .30-caliber bullet from a pulmonary vein to the left atrium, where it lodged. A foreign body lying free in one of the cardiac chambers or great vessels is considered an indication for surgical intervention[25-27] when carried out under controlled conditions by an experienced surgeon. Embolization, sepsis, erosion, and vascular occlusion (in the case of intravascular foreign bodies) are the major complications that must be prevented.

Thrombi may arise in the cardiac chambers as a result of injury to the endocardium. Suture material[54] used in the operative repair of a penetrating cardiac wound may, if it penetrates the endocardium, become a nidus for thrombus formation. Similarly, a missile foreign body in the endocardium may be a focus for thrombus formation. In a patient in our series a retained shell fragment in the right ventricular myocardium was the

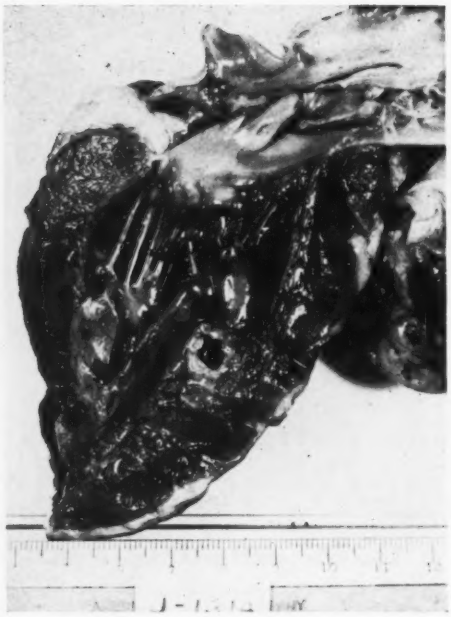

FIG. 8. Dissection of heart, case 4, revealing a metallic foreign body embedded in the base of the anterior papillary muscle and surrounded by a ring of necrotic tissue.

nidus for mural thrombus formation that led to multiple pulmonary embolization with death 3 weeks after injury.

Infection

With penetrating cardiac wounds, especially missile wounds, the incidence of contamination is high. Harken[25] reported that culture of missiles acting as foreign bodies in the heart or great vessels demonstrated pathogenic bacteria in 67 per cent. Other foreign material such as clothing accompanied 30 per cent of the missiles. Valle[12] reported a similar incidence of contamination. Harken and Zoll[27] were able to culture pathogenic organisms from 3 of 4 interatrial foreign bodies. Before antibiotics became available, infection was the commonest and most serious complication of penetrating heart wounds, and even now acute or subacute bacterial endocarditis may be a sequela and septic thrombi may become embolic from the heart. In our series, clinical or pathologic evidence of infection resulting directly from an intramyocardial foreign body was encountered in only 4 instances. The complex problems of sepsis incident to penetrating injuries are demonstrated in the following case.

Case 4. AFIP Acc. 329470: A 19-year-old soldier in Korea was wounded in the left chest by a mortar shell fragment. The immediate course was uneventful, despite the shell fragment that x-ray studies demonstrated in the myocardium of the left ventricle. Penicillin was administered parenterally; 3 days later he was evacuated to an Army General hospital. After admission his temperature varied from 101 to 103 F. and his pulse rate from 96 to 100 per minute. Physical examination revealed signs suggestive of pneumonitis of the left lung. He continued to have a low grade fever and 6 days after injury he complained of headache, became semicomatose, nuchal rigidity and horizontal nystagmus developed, and his temperature rose to 105 F. Spinal fluid was purulent and under increased pressure, but organisms were not identified on direct smear. A diagnosis of purulent meningitis, type unknown, was made and the dosage of penicillin was increased. The following day the patient became dyspneic and cyanotic, a ventricular gallop rhythm was noted, and moist rales were heard throughout both lung fields. Shortly thereafter fulminant pulmonary edema developed and the patient died. Postmortem examination revealed hemopericardium of 50 ml. and fibrinous pericarditis. On the lateral border of the left ventricle, 5 cm. from the apex, there was a soft area, 8 mm. in diameter, covered with a heavy fibrinous exudate. From this area a necrotic tract that admitted a probe led to a metallic fragment embedded in the anterior papillary muscle and surrounded by a zone of necrotic tissue (fig. 8). A small amount of thrombotic material was adherent to the trabeculae carneae between the anterior papillary muscle and the anterolateral wall of the ventricle. Ecchymoses up to 2 mm. in diameter were scattered over the interventricular septum and lateral wall of the left ventricle. Septic meningitis was evident, and microabscesses of the brain had resulted from septic emboli. Small abscesses were seen in the liver and kidneys. Cultures of the abscesses yielded *Klebsiella pneumoniae*. Histologic study of the myocardium revealed interstitial inflammation and microabscesses.

Structural Defects

Structural defects of the heart resulting from penetrating wounds have interesting pathologic as well as clinical features. The structural lesion most often referred to in

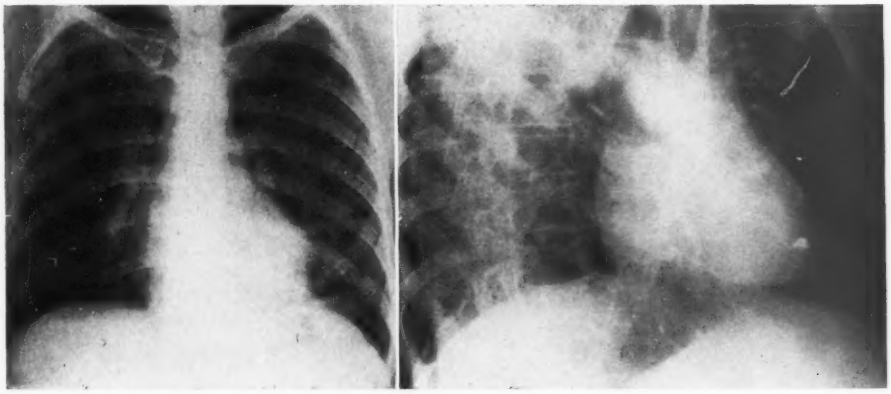

FIG. 9 *Left.* Case 5. Postero-anterior chest roentgenogram demonstrating a small aneurysm of left ventricle at site of entrance of the shell fragment. The fragment is not visible as it is superimposed over the vertebral column.

FIG. 10 *Right.* Case 5. Venous angiocardiogram in right anterior oblique position with opacification of the right ventricle showing the retained shell fragment in the right ventricular myocardium.

the literature is aneurysm formation with or without rupture. Probably the case of aneurysm formation with rupture reported by Fisher[3] in 1886 and later emphasized by Ballance[1] served as a start for such reasoning. Loison[55] is cited by several writers[10, 20] as having reported 9 instances of aneurysm formation and rupture among 254 cases of heart injury as early as 1899, but he did not indicate clearly what type of cardiac injury predisposed to rupture. Klose[56] again described the phenomenon in 1923. In reality, this complication has been overemphasized. Rupture has been reported within the first few hours or days after an extensive penetrating or perforating injury, after myocardial infarction incident to traumatic coronary occlusion, and most often after a contusive injury of the myocardium. Most of these cases could hardly be classified as examples of true aneurysm formation followed by rupture, and actually the sequence must be extremely rare. A fairly complete perusal of the English literature of the last 25 years has failed to reveal a single substantiated instance. Several surgeons[27, 57] have reported cases of aneurysm formation in the presence of a retained intramyocardial missile, in which it is possible that rupture would have been imminent if removal of the fragment and repair of the myocardium had not been accomplished. In our series of penetrating heart wounds, there is not a single example of rupture of an aneurysm secondary to a retained intramyocardial foreign body.

Aneurysm formation is not rare. In many instances a reversal of the direction of movement of the myocardium in the area immediately surrounding the retained fragment may be demonstrated by roentgenokymographic study.[37] Occasionally the aneurysm may be apparent on routine roentgen study, as in case 5.

Case 5. This 32-year-old man was wounded in action on July 30, 1950, by a shell fragment that penetrated the left anterior chest wall. Left hemothorax developed. Soon after injury a loud systolic murmur and thrill were noted over the precordium. Symptoms consisted of chest pain of an intermittent constrictive type, moderate external fatigue, and shortness of breath. Examination revealed a harsh grade IV systolic murmur heard maximally at the third and fourth intercostal space at the sternal border and widely transmitted. Electrocardiogram showed QRS changes suggesting minimal intraventricular conduction disturbance. Chest x-ray (fig. 9) and a venous angiocardiogram (fig. 10) revealed a metallic foreign body in the wall of the right ventricle and an aneurysm of the left ventricle. At thoracotomy

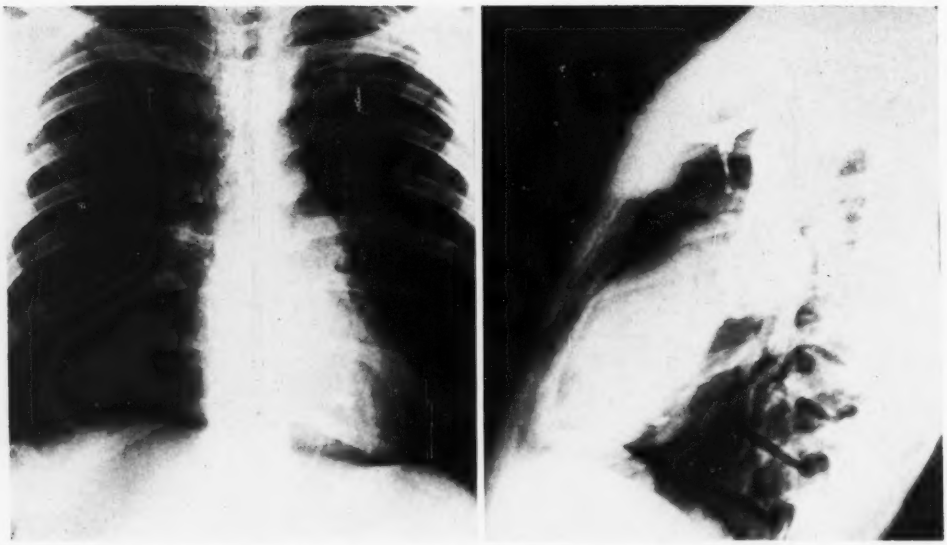

FIG. 11 *Left.* Case 6. Postero-anterior chest roentgenogram demonstrating retained shell fragment in the myocardium.

FIG. 12 *Right.* Case 6. Venous angiocardiogram showing opacification of the right side of the heart and the foreign body in the left ventricular myocardium.

the foreign body was removed from the right ventricle and the presence of an aneurysm of the left ventricle was confirmed. The postoperative course was uneventful. Cardiac catheterization revealed evidence of a left-to-right shunt at the ventricular level compatible with an interventricular septal defect. The data indicated that the fragment passed through the left ventricular wall and interventricular septum, and lodged in the right ventricular myocardium.

By far the most interesting feature in this case is the demonstration of a traumatic interventricular septal defect in a patient who survived a perforating wound of the heart. Many instances of perforating missile wounds to the heart without immediate fatality,[1, 10, 58-60] and several with recovery,[10, 46, 61] have been recorded. To our knowledge case 5 is the first reported case in which the patient survived a traumatic interventricular septal defect produced by a perforating missile wound.

An equally interesting example of a structural defect incident to a penetrating missile wound is case 6.

Case 6. This 20-year-old man was wounded in action on September 21, 1950, by a shell fragment that penetrated the chest in the fourth right intercostal space parasternally. Right hemothorax developed, necessitating thoracentesis. A continuous murmur, maximal at the right fourth intercostal space along the sternum, was noted 2 weeks after the injury. The patient was returned to duty and was asymptomatic except for occasional chest pain and mild dyspnea during strenuous exertion. Examination at Walter Reed Army Hospital in 1952 revealed the continuous murmur previously described. The electrocardiogram showed minimal nonspecific T-wave abnormalities. Roentgen examination (fig. 11) demonstrated a metallic foreign body in the myocardium. At thoracotomy, performed in the expectation of finding an arteriovenous fistula of the internal mammary artery, a thrill over the heart at the atrioventricular junction was palpated, but the pericardium was not opened as the surgeon interpreted the finding as indicative of an interventricular septal defect. Cardiac catheterization performed postoperatively revealed a left-to-right shunt at the right atrial level.

A venous angiocardiogram (fig. 12) localized the shell fragment within the left ventricular myocardium. Retrograde aortography (fig. 13) demonstrated a large tortuous coronary vessel considered a result of coronary arteriovenous fistula. Since

he patient has remained relatively asymptomatic, onservative management with periodic observaion continues.

Comment. It is our impression that this patient has a traumatic coronary arteriovenous fistula. Coronary arteriovenous fistula has seldom been reported[62, 63] and usually has been considered of congenital origin. A lesion similar to a fistula of the sinus of Valsalva or one resembling that recorded by Gerbode,[64] in which a penetrating wound produced a right atrial subaortic fistula cannot be definitely excluded.

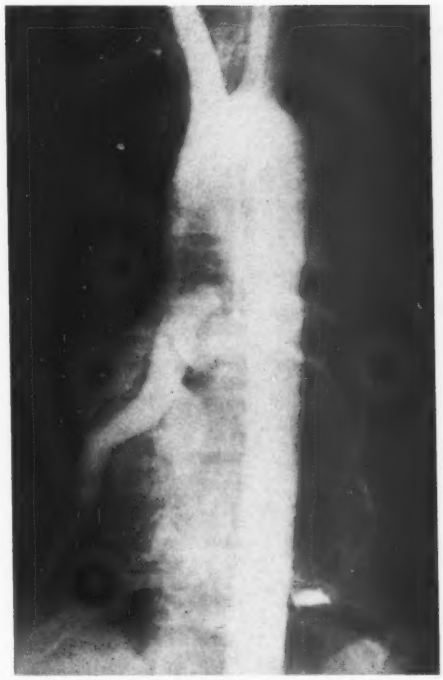

FIG. 13. Case 6. Retrograde aortogram performed by Dr. Andrew G. Morrow, National Institutes of Health, Bethesda, Maryland, demonstrating probable coronary arteriovenous fistula.

Injury of Heart Valves

The involvement of the cardiac valves in penetrating wounds of the heart is relatively rare, particularly so when the patient survives. Undoubtedly the flexibility of these structures accounts in part for their ability to escape injury. Usually when they are involved the wound is so extensive that death is rapid. A unique case of mitral insufficiency due to a bullet wound that involved the anterior leaf of the mitral valve has been reported by Adam.[65] Of interest is the report by Lowen and others[66] in which the heart was transfixed to the spine by an ice pick that perforated the anterior leaf of the mitral valve. In our series there are several instances of penetrating missile wounds involving the heart valves and in all death ensued within several days of injury. An exception was a case in which a needle penetrated the myocardium and lodged in the mitral valve. Death from congestive failure occurred a year after injury. A half century ago, needles were one of the commonest causes of penetrating wounds of the heart, and many instances have been reported[67] in which the needle was retained. In Decker's series of 100 cases,[20] 18 of the retained foreign bodies in the heart were needles and several involved a cardiac valve.

Arrhythmias and Conduction Defects

Penetrating heart wounds may present primarily as disturbances of cardiac rhythm or conduction. The entire gamut of arrhythmias or conduction defects may be represented, their character usually depending upon the site of injury. A wound of the atrium has, in several of our cases, produced atrial fibrillation or other supraventricular arrhythmia. Various degrees of atrioventricular block and bundle-branch block have also been observed. In some instances cardiac asystole or ventricular fibrillation has been suspected as the cause of death, but this has not been proved.

Electrocardiographic Aspects

Frequently the electrocardiogram may offer the main objective evidence of cardiac injury by a penetrating wound. The significant features of the electrocardiography of penetrating heart wounds have been well presented.[68–70] Perhaps most characteristic is the wide diversity of the possible changes.

Conduction disturbance and arrhythmias have been mentioned. Of course, there is nothing in the tracing that would indicate that trauma was responsible for the injury. In the presence of a retained foreign body, the electrocardiogram is often normal, or it may reveal nonspecific ST- and T-wave abnormalities, which are compatible with a large number of pathologic conditions. Pericardial-epicardial injury and particularly hemopericardium are often responsible for the abnormalities, and these are the ones most commonly encountered. The changes of ischemia, injury, and muscle death characteristic of coronary artery disease with myocardial infarction may be duplicated with penetrating heart wounds, but are relatively rare unless the injury is extensive, a coronary artery is severed, or coronary thrombosis due to trauma results in myocardial infarction. The coronary artery most often injured is the left, especially its anterior descending branch, and the changes are those of anteroseptal myocardial infarction. A major coronary artery may be severed without producing significant electrocardiographic changes.[71]

Part II.

Penetrating Injuries of the Aorta

Penetrating wounds of the aorta have received relatively little attention in the medical literature. Although many articles concerned with penetrating wounds of the heart or peripheral arteries include examples of penetration of the aorta, they constitute but a small percentage of the number reported. However, injury of this type is sufficiently distinctive to merit individual consideration.

Penetrating injuries of the aorta first received notable attention after World War I, when Makins[58] published a résumé of gunshot injuries involving the heart and great vessels, as exemplified by specimens on exhibition in the Museum of the Royal College of Surgeons. Included were cases demonstrating penetrating wounds of the aorta that were not immediately fatal and an example of false aneurysm formation incident to such an injury. In 1922 Dshanelidze,[72] a Russian, successfully sutured a penetrating wound of the thoracic aorta and he has been credited as the first to report this surgical feat. Blalock,[73] in 1934, was the second. His patient was an 18-year-old Negro who had been wounded in the intrapericardial portion of the ascending aorta with an ice pick. Blalock pointed out that the location of the wound was unusual, since this part of the aorta is protected by the sternum. His experience with animals had demonstrated that even small wounds in this part of the aorta are usually fatal; for example, a wound 3 mm. in length in the aorta often caused death, while in the pulmonary artery it was seldom fatal. By 1952 Beattie and Greer[74] were able to find 4 reports of successful surgical repair of a penetrating wound of the aorta and added a fifth. Harken,[25] in recounting the experience of the Thoracic Unit of the 160th General Hospital in World War II, reported 78 cases in which missiles penetrated or injured the great vessels, and, of these, 29 involved the aorta. He emphasized the association of infection with these penetrating missile injuries, stating that approximately 15 per cent were accompanied by abscess formation. The Korean hostilities again focused attention on traumatic injuries of the major arteries, and the surgical experience gained in that conflict has led to a better understanding of traumatic arterial lesions, the problems and surgical technics of their management being applicable to certain aspects of the management of penetrating injuries of the aorta.[75, 76]

Our purpose here is to present cases of penetrating wounds of the aorta as a distinct group in our series. The clinical problems of aortic injury of this type must be considered independently if diagnosis is to be accurate and surgical treatment effective. Thus, emphasis will be placed on the clinical course of these lesions and the necessity for prompt surgical treatment. The surgical technics employed are beyond the scope of

is discussion and have been well presented sewhere.

Penetrating injury of the aorta, exclusive combined cardiac and aortic wounds, was ncountered in 66 cases of this series. Of ese, 46 were caused by missiles and 20 by ab wounds. The usual result of such in-ry was rapid exsanguination, and in some stances penetration of the aorta within the ericardial sac soon led to fatal cardiac mponade. However, sudden or swift death as not always the consequence, for 13 pa-ients (19.6 per cent) survived the imme-liate postinjury period. We have reviewed he course of these patients for the purpose f formulating and adopting effective methods f treatment.

Formation of False Aneurysm

A complication of penetrating injury of the aorta that permitted limited survival was development of a false aneurysm in 5 patients. The symptoms and signs of an enlarging mass, varying with the location of aortic injury, usually preceded eventual rupture of the aneurysm. Rupture into a bronchus caused the death of 1 patient 70 days after injury, and rupture into the gastrointestinal tract, that of another after 16 days' survival. The 3 other patients with false aneurysms lived 12, 32, and 70 days, respectively, before terminal rupture. The typical course of events from development to rupture of a traumatic false aneurysm are illustrated by Case 7.

Case 7. AFIP Acc. 152493: A 28-year-old white man was wounded in the epigastrium by a shell fragment. Laparotomy revealed a perforation of the liver and scattered hemorrhages throughout the gastrointestinal tract but no perforation of the bowel. Convalescence was uncomplicated except for pain in the left sacroiliac and lumbar regions, which came on 4 days after the injury. Nineteen days later an episode of severe pain on the left side of the abdomen with radiation to the genitalia was diagnosed as possible renal colic. The acute pain subsided and the patient became ambulatory, complaining only of mild, persistent lumbar pain. Examination 6 weeks after the injury revealed a small draining sinus of the epigastric region and tenderness of the left lumbar area, where he also felt pain on raising his left leg. Roentgen studies of the abdomen, including retrograde pyelograms, disclosed a mass and 2 small shell fragments in the left psoas region. Sixty-six days after injury a demonstrable mass appeared suddenly in the left lower abdomen, along with fever, leukocytosis, and signs of shock. The left femoral pulse could not be felt. A diagnosis of ruptured abdominal aneurysm was made, but operative intervention was not attempted. Supportive treatment including transfusion was to no avail; the patient suffered increasingly severe pain, his hemoglobin level dropped rapidly to 27 per cent, and profound shock ensued. The patient died 70 days after in-

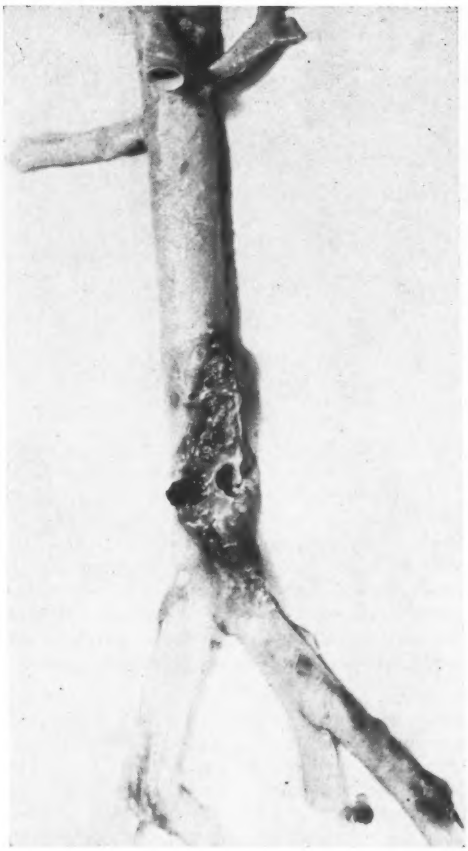

FIG. 14. Case 7, AFIP 152493. Abdominal aorta dissected free at autopsy, revealing an irregular laceration with endothelialized edges, surrounded by a zone of thickened, partially organized hemorrhage. Note shell fragment impinging on aortic wall just to right of the laceration.

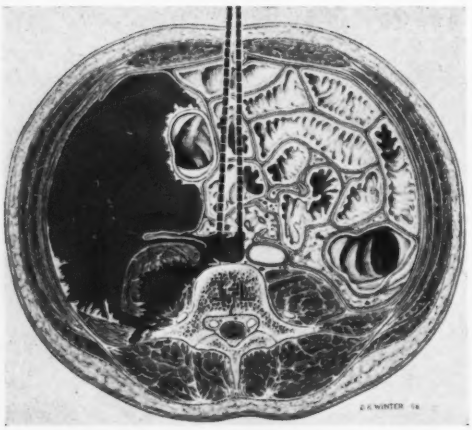

FIG. 15. Case 7. Diagram of a transverse section of the body at the level of the third lumbar vertebra, illustrating the course of the two shell fragments (*dotted line*) and the extent of retroperitoneal dissection caused by hemorrhage from the initial false aneurysm. One shell fragment impinged on the aortic wall and the second lacerated the left lateral aspect of the aorta coursing through the left psoas muscle. The lacerated psoas muscle served to contain the initial false aneurysm formation.

jury. On postmortem examination there was serohemoperitoneum of 1,500 ml. The abdominal viscera were displaced by a huge mass, covered by parietal peritoneum, that extended from the brim of the pelvis to the diaphragmatic attachment and from the vertebral column to the left lateral abdominal wall. The mass contained a recent clot of 1,500 ml., and when this was evacuated a second mass was seen within the left psoas major muscle. This mass was fusiform, about the size of a lemon, and contained organized clot. It was connected with a defect in the abdominal aorta just proximal to the iliac vessels (fig. 14). The course of the shell fragments that produced this perforation as well as the resultant false aneurysm formation is shown in the diagram (fig. 15).

Another complicating lesion of traumatic vascular injury besides false aneurysm formation is the development of an arteriovenous fistula. The development of such a fistula secondary to aortic injury must be extremely rare, although it is a common complication of wounds of other major arteries. In a recent comprehensive report[77] not a case involving the aorta was mentioned. None of the patients with aortic injuries in our series developed an arteriovenous fistula.

Thrombotic Occlusion of the Wound

A laceration or perforation of the aort may be temporarily occluded by thrombu formation that may undergo organizatio thus permitting survival of the injured pe son. It is probable that an appreciable nun ber of patients have survived small penetra ing injuries of the aorta with so few sig or symptoms that the lesion could not l recognized clinically. The rapid sealing ov of the perforation by thrombus formation probably facilitated by the elasticity of th aorta. Occlusion of the site of a penetratin wound of the aorta was observed in severa instances in our series.

Thrombotic occlusion of a penetratin wound of a great vessel is seldom permanent Days later a massive hemorrhage may occu from the site of the wound, as demonstrate in the following case.

Case 8. AFIP Acc. 108737: A 32-year-old Negro was admitted to the hospital unconscious, having fainted after being stabbed several times in the chest with a pocket knife. He soon recovered consciousness. The wounds were probed and thought to be superficial. The patient's condition remained good and no signs or symptoms of serious injury developed. Two days later he was discharged from the hospital and returned to his usual heavy manual labor. He remained asymptomatic until 8 days after he was wounded, when he suddenly collapsed at work, had convulsions, and died. At autopsy the cause of death was found to be hemopericardium of 300 ml. of fluid and clotted blood. On the anterior surface of the parietal pericardium, directly beneath the healed laceration to the right of the sternum, there was a laceration, 0.5 cm. in length, which contained an organized thrombus surrounded by hemorrhagic connective tissue. On the visceral pericardium near the junction of the ascending and transverse arch of the aorta was a perforating laceration of the aorta, 0.8 cm. in length, containing thrombus. Another laceration, 1.8 cm. in length, extended through the inferior portion of the arch of the aorta into the adjacent pulmonary artery, producing a 1.3-cm. defect (fig. 16). The latter also penetrated both walls of the pulmonary artery and the visceral pericardium overlying the left atrium, where there was an organized thrombus. The atrium was not penetrated.

Persistent Hemorrhage

Hemorrhage of varying degree is a feature

of every penetrating wound of the aorta. If the wound be large, massive hemorrhage and death may be expected. Smaller lacerations or perforations, even including some 0.5 cm. in diameter, may result in false aneurysm formation or be occluded by a thrombus. Nevertheless, smaller penetrating wounds of the aorta frequently continue to be a source of persistent hemorrhage. Where the wound is small and not occluded, the hemorrhage may be slow but nonetheless formidable and often persistent. Consequently, in every individual with a penetrating wound and evidence of continuing unexplained hemorrhage, the possibility of a penetrating wound of the aorta must be considered. The following case demonstrates this circumstance.

Case 9. AFIP Acc. 320696: A 38-year-old man was admitted to the hospital in shock after having been shot in the left side of the chest with a 4.10-gage shotgun. Blood pressure was 50/0 mm. Hg. Chest roentgenograms revealed multiple shot in the left upper thorax. Transfusion of 500 ml. of plasma and 1,000 ml. of whole blood raised the blood pressure to 120/80 with a pulse of 100 per minute. Bleeding at the site of the wound was profuse. A left thoracentesis produced 360 ml. of blood. Because of the extent of the wound and the state of the patient, it was decided to treat him by blood replacement and thoracentesis in the hope that the hemorrhage would subside. During the ensuing 8 hours 4,500 ml. of whole blood were administered and 1,500 ml. were removed by 3 thoracenteses. Thoracotomy was then performed. The upper lobe of the left lung was a solid hematoma and the mediastinum was filled with hemorrhage and recent clot formation. The fourth intercostal artery was bleeding and therefore was ligated. After the operation was completed, bronchoscopy was attempted, but during the procedure cardiac arrest occurred.

At autopsy the site of the persistent hemorrhage was found to be a perforation of the aorta, approximately 1 mm. in diameter, in the lateral aspect of the descending portion of the aortic arch.

Management

Penetrating lesions of the great vessels, the aorta in particular, have been successfully treated by surgical repair. Recent experimental studies[78] have defined the pathologic characteristics of missile injuries of the aorta and other large arteries, particularly as they influence surgical efforts at repair. Although few reports have concerned penetrating injuries to the aorta, the surgical technics described for the treatment of penetrating injury of other major arteries also apply to the aorta. The use of arterial grafts and recent advances in anesthesia, particularly hypothermia, have increased the surgeon's ability to repair injuries of this type.

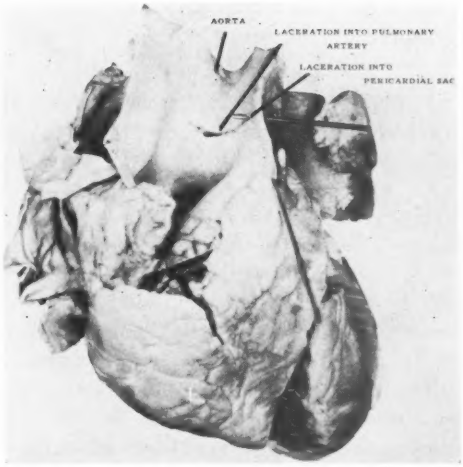

FIG. 16. Case 8, AFIP 108737. The heart with aorta opened to show the site of the perforating wound and the extent of laceration from aorta into the pulmonary artery.

In contrast to the management of penetrating injuries of the heart, a conservative medical approach has no place in the treatment of penetrating wounds of the aorta and other great vessels, except that supportive measures must be taken to sustain the patient until surgical repair can be attempted. To delay surgical intervention in a patient with penetrating aortic injury invites fatal hemorrhage, or, if the lesion be intrapericardial, cardiac tamponade. False aneurysms may develop in those who survive the immediate effects of injury, but rupture of such aneurysms is the probable sequel, and surgical repair should not be delayed. Spontaneous occlusion of an aortic laceration by thrombus formation produces temporary but treacherous repair, for subsequent hemorrhage may dislodge the thrombus or lead to the formation

of a false aneurysm which eventually will rupture.

Summary and Conclusions

1. Immediate survival from penetrating traumatic injuries to the heart or aorta may be expected in roughly 15 per cent of the cases, a figure derived from the postmortem statistics of 456 cases. However, clinical experience suggests that approximately 1 out of 4 individuals with a penetrating heart wound will survive the immediate effects of wounding and most will live long enough to reach adequate medical care. Penetrating injury of the aorta carries a grave prognosis, but approximately one-fifth of the wounded (19.6 per cent in this series) may be expected to survive the immediate effects of injury. Present statistics indicate that a 30 per cent mortality may be expected in this group of initial survivors. An appraisal of the clinical, diagnostic, and therapeutic problems presented by this group suggests that the majority can be saved.

2. Review of the immediate clinical problems and management of penetrating heart wounds indicates that a conservative therapeutic approach, including pericardiocentesis, may be successful in permitting recovery. Under certain specific circumstances, however, therapy of this kind is inadequate and surgical treatment is essential.

3. The late complications and sequelae of penetrating heart wounds, particularly missile wounds, are described with reference to the diagnosis and proper therapeutic approach. In particular, the criteria for surgical removal of a retained foreign body within the heart are critically reviewed and the hazards of unnecessary surgical intervention emphasized.

4. In penetrating injury of the aorta, death may be delayed if the penetrating wound becomes occluded by a thrombus or if false aneurysm formation develops. Should the penetrating wound be small, a relatively slow but persistent hemorrhage may occur, which, if uncorrected, will be lethal.

5. Conservative medical management of penetrating injury of the aorta is not warranted and surgical intervention should b immediate. Delay may result in fatal hem orrhage from a site of persistent bleeding o from dislodgment of a thrombus or ruptur of a false aneurysm.

Summario in Interlingua

1. Superviventia immediate post penetra te lesiones traumatic del corde o del aort pote esser expectate in approximativement 15 pro cento del casos. Iste valor es derivat ab le statisticas necroptic de 456 casos. Tan en, le experientia clinic suggere que circa ex 4 individuos con vulneres penetrante l corde supervive al effectos immediate del le sion e que le majoritate de istes vive sati longe pro attinger adequate attention medi cal. Vulnere penetrante le aorta ha un prog nose grave, sed circa un quinto del victima (19,6 pro cento in le supra-mentionate serie) supervive al effectos immediate del accidente. Le statisticas nunc disponibile indica que on debe expectar un mortalitate de 30 pro cento in le gruppo de superviventes initial. Le evalutation del problemas clinic, diagnostic, e therapeutic que es presentate per iste gruppo suggere que le majoritate de tal patientes pote esser salvate.

2. Un revista del immediate problemas cline e del methodos de tractamento in casos de penetrante vulneres cardiac indica que un attitude de conservativismo therapeutic, con le inclusion de pericardiocentese, pote succeder a effectuar le restablimento del patiente. Tamen, sub certe specific circumstantias, therapia de iste genere es inadequate e un intervention chirurgic deveni essential.

3. Le tardive complicationes e sequellas de penetrante lesiones cardiac—specialmente de lesiones per projectiles—es describite con referentia al diagnose e al correcte tactica therapeutic. In particular, le criterios applicabile al elimination chirurgic de un corpore estranie que remane intra le corde es discutite criticamente, e le hasardos de innecessari interventiones chirurgic es signalate.

4. In casos de vulneres penetrante le aorta un retardo del morte pote resultar si le vulnere es occludite per un thrombo o si un

false aneurysmo es formate. Si le vulnere penetrante es micre, il pote occurrer un relativemente lente sed persistente hemorrhagia, isto—si non corrigite—deveni mortal.

5. Le conservative tractamento medical de vulneres penetrante le aorta non es justificate. Intervention chirurgic debe esser effectuate immediatemente. Omne retardo pote devenir le causa de un hemorrhagia mortal ab le sito de un sanguination persistente o ab le displaciamento de un thrombo o le ruptura de aneurysmo false.

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Kessler, R. H., Lozano, R., and Pitts, R. F.: Studies on Structure Diuretic Activity Relationships of Organic Compounds of Mercury. J. Clin. Invest. **36**: 656 (May), 1957.

All of the compounds studied were accumulated in the kidneys. However, there was no obvious relation between site or concentration and diuretic activity. Compounds that were not diuretic were slowly excreted. Certain in vitro inhibitors of sulfhydryl enzymes did not prove to be diuretic. If sulfhydryl inhibition is important in diuresis, compounds that are effective must have different properties from those studied in these experiments. Diuresis probably depends on a fundamental structure; based on the compounds studied it appears that there must be at least a 3 carbon chain included. This chain must have a terminal mercury atom with a hydrophilic group at least carbon atoms distant.

Oppenheimer

ABSTRACTS

ATHEROSCLEROSIS

Havel, R. J.: Early Effects of Fasting and of Carbohydrate Ingestion on Lipids and Lipoproteins of Serum in Man. J. Clin. Invest. **36**: 855 (June), 1957.

Very low density lipoproteins decreased consistently in serum after 400 Gm. of glucose were taken by mouth during a 4-hour period. These levels were lower than those of fasting controls. All lipid fractions of this lipoprotein were reduced. Percentage reduction was greatest for triglycerides and least for cholesterol. Phospholipids were reduced an intermediary amount.

OPPENHEIMER

Havel, R. J.: Early Effects of Fat Ingestion on Lipids and Lipoproteins of Serum in Man. J. Clin. Invest. **36**: 848 (June), 1957.

After fat ingestion the increase in serum triglycerides is due entirely to an increase in their concentration in low-density lipoproteins. Cholesterol and phospholipid in this fraction are also increased. The greatest increase was observed 4 hours after fat was taken by mouth. Serum phospholipid was increased after a fatty meal and remained high longer than did the triglycerides. Very low and high-density lipoprotein fractions participated in this increase. The slow return to control values was based on high-density lipoproteins, which remained elevated even though lipemia was no longer present. Serum cholesterol increased only slightly after fat ingestion.

OPPENHEIMER

Selye, H.: Protection by Pregnancy against the Development of Experimental Arteriosclerosis and Metastatic Calcification. Am. J. Obst. & Gynec. **74**: 289 (Aug.), 1957.

The administration of dihydrotachysterol (AT-10) to rats produced Mönckeberg sclerosis-like changes in the arterial system and metastatic calcification in heart, stomach, and muscles. In these experiments, AT-10 was administered to female albino Wistar rats in both gravid and nongravid states. The latter group was found to be moribund and emaciated at the end of the experimental periods. Severe arteriosclerosis and ectopic calcium deposits were observed in various organs. The pregnant animals were found to be in excellent health with little evidence of vascular disease at autopsy. The mechanism whereby pregnancy protects the animals from the toxic effects of AT-10 is unknown. It is suggested that further study of this phenomenon may provide information concerning the factors in pregnancy that afford protection against damage to mesenchymal tissues.

SHUMAN

BLOOD COAGULATION AND THROMBOEMBOLISM

Mustard, J. F.: Increased Activity of the Coagulation Mechanism during Alimentary Lipaemia: Its Significance with Regard to Thrombosis and Atherosclerosis. Canad. M. A. J. **77**: 308 (Aug. 15), 1957.

The effect of alimentary lipemia on the blood clotting mechanism in vivo was studied in 24

subjects by means of measuring various coagulation factors before and after eating a meal containing 72 to 76 Gm. of animal fat. Postprandially, the Russell viper venom time (which was taken to indicate the activity of lipid coagulation factors) decreased in 22 individuals; the blood clotting time in silicone, the platelet count, and the antihemophilic globulin content decreased in 23; and the Christmas factor activity increased in 23. Dicumarol administration counteracted the acceleration of coagulation in 7 of 9 subjects, an effect attributed to reduction in Christmas factor activity. The possible atherogenic propensity of this enhanced coagulation state is discussed.

ROGERS

Houcke, E., Merlen, J. F., and Jaillard, J.: On Massive Intracavitary Cardiac Thrombosis. Arch. mal. coeur **50**: 104 (Feb.), 1957.

In more than 800 routine autopsies, massive thrombosis of all cardiac cavities was found 3 times (in 1 patient with chronic cor pulmonale and in 2 with mitral stenosis). All were in congestive heart failure. The thrombus was of gelatinous consistency, contained red pigment and fibrin, and was in intimate contact with other, organized thrombi. It was probably formed during the last minutes of life.

LEPESCHKIN

Friese, G., and Rotzler, A.: Contribution to the Study of the "Young Female Arteritis Variety" of the Aortic Arch Syndrome (Pulseless Disease). Ztschr. Kreislaufforsch **46**: 353(May), 1957.

In the first patient, a 30-year-old woman, death due to cerebral thrombosis took place only 4½ months after the appearance of the first symptoms. Autopsy showed fresh and organized thrombi in all branches of the innominate artery without endothelial changes or increased blood coagulation. In the second patient, a 19-year-old woman, the greatly elevated erythrocyte sedimentation rate became much smaller during treatment with Butazolidin. The third patient, a 39-year-old man, showed absence of pulsation in the foot arteries in addition to the aortic arch syndrome, and could therefore have had generalized arterial disease.

LEPESCHKIN

Beaumont, J. L., Moeri, E., Lenègre, J.: Results of Anticoagulant Treatment in Mitral Disease, Based on 1400 Observations. Arch. mal. coeur **50**: 225 (March), 1957.

Of 1,400 patients with mitral disease, 666 received preventive anticoagulant treatment for more than 8 days. The mortality due to thrombosis was only 1.5 per cent among these patients, while it was 6.6 per cent among nontreated persons; thromboembolic complications were 1.2 per cent and 7.1 per cent in the 2 groups. Among 371 persons subjected to mitral commissurotomy, fresh atrial thrombosis was found during the operation 3 times as often in nontreated as in treated patients. The incidence of embolic complications during regularization of atrial fibrillation in 336 persons was 5.7 per cent among the nontreated and only 0.37 per cent among the treated patients. Thrombosis occurred during treatment of right heart failure (720 persons) in 9.4 per cent of the patients without anticoagulant treatment but in only 1.6 per cent of the persons receiving this treatment. Hemorrhages appeared in 4.3 per cent of the treated patients; they were usually benign, but led to death in 0.39 per cent. One additional patient died in heparin shock.

LEPESCHKIN

CONGENITAL ANOMALIES

Niedner, F. F., and Kaatz, H. G.: Anomalous Venous Return to the Heart. (Diagnosis and Surgical Possibilities.) Cardiologia **30**: 173 (March), 1957.

The authors demonstrated on 6 examples a method of superposition of roentgenograms of different pathways of cardiac catheters that can be used, in addition to usual procedures, to differentiate complex cardiac malformations. The method proved particularly valuable in excluding, in the presence of large atrial septal defects, an abnormal connection of the pulmonary veins, or to demonstrate its presence in cyanotic cases in addition to a ventricular septal defect or other lesions. Four principal groups of pulmonary venous anomalies were distinguished on the basis of the number and the site of the vessels involved in the transposition. Surgical approaches feasible for each group are described. The best criterion for success of a corrective procedure is the postoperative reduction in the size of the right atrium.

PICK

Weidman, W. H., Swan, H. J. C., DuShane, J. W., and Wood, E. H.: A Hemodynamic Study of Atrial Septal Defect and Associated Anomalies Involving the Atrial Septum. J. Lab. & Clin. Med. **50**: 165 (Aug.), 1957.

Hemodynamic data obtained from 71 patients with an interatrial communication were presented. Of these patients, 44 were considered to be examples of uncomplicated atrial septal de-

feet, 13 had associated pulmonary hypertension, 6 had anomalous connection of one or more pulmonary veins, 6 had persistent common atrioventricular canals, and 2 had mitral valve disease. In the patients without pulmonary hypertension the pulmonary blood flow was greatly increased (average 8.3 L./min./M.) due to the presence of left-to-right shunting of considerable degree. In a number of these patients it was demonstrated that of the blood shunted left to right, a greater proportion originated from the right lung than from the left lung. Small right-to-left shunts without hemodynamic significance were shown to exist frequently, and of the blood shunted right to left a greater proportion was of inferior caval than of superior caval origin. In these patients the systemic blood flow was normal. The majority of patients with severe pulmonary hypertension had pulmonary and systemic flows of reduced magnitude. In 2 patients with severe pulmonary hypertension a large pulmonary blood flow was calculated.

Patients with anomalous connection of one or more pulmonary veins or with common atrioventricular canal may show the same fundamental circulatory disorder as patients with an atrial septal defect of the usual type. The frequency and practical importance of each of these lesions are compelling reasons that they be sought and diagnosed preoperatively. Highly suggestive evidence for each of these lesions may be obtained from critical analysis of the oxygen saturation of separate series of samples of blood drawn from different locations in the right ventricle, right atrium and both venae cavae. Differences of some magnitude may exist between samples drawn at random from these sites, but considerable significance may be placed on a difference that is consistently demonstrated. A significant correlation was demonstrated between the pressure gradient across the pulmonary valve frequently found in these patients and the magnitude of the pulmonary blood flow. The gradient did not appear to be associated with a pathologically significant degree of pulmonary stenosis.

MAXWELL

Dubost, C., Cozanet, P., de Balsac, R. H., Lenfant, C., Passelecq, J., Guéry, J., and Weiss, M.: Anomalous Right Pulmonary Venous Drainage with Interatrial Septal Defect. Subdivision of Right Atrium under Extracorporeal Circulation. Recovery. Arch. mal. coeur **50**: 155 (Feb.), 1957.

A 9-year-old girl with slight cyanosis and dyspnea showed a split first and accentuated second sound, while the electrocardiogram showed right axis deviation with deep Q and S waves in lead III, tall notched R waves in V_{3r} - V_3, very deep S waves in V_6, and inversion of the T wave up to V_5. Roentgenologically the heart was enlarged to the left, with a prominent right atrium and a long pulmonary conus. Angiocardiography showed long persistence of the dye in all cardiac cavities. Cardiac catheterization disclosed a large oxygen difference between superior vena cava and right atrium; the catheter entered the right upper pulmonary vein. The ether test was positive. During the operation hypothermia and a pump-oxygenator were used. It was found that the 3 upper right pulmonary veins entered the right atrium (1 of them at the origin of the superior vena cava), and that a large atrial septal defect was present. The anterior wall of the right atrium was stitched to the anterior edge of the atrial septal defect, so that the entire pulmonary venous drainage was channeled into the left atrium, leaving enough room for passage of caval blood through the anterior half of the right atrium. The child left the hospital after 3 weeks.

LEPESCHKIN

Michel, D., Herbst, M.: An unusual anomaly of a Coronary Artery. Ztschr. Kreislaufforsch. **46**: 538 (July), 1957.

An 8-year-old girl showed mild cyanosis, electrocardiographic signs of right ventricular hypertrophy with normal P waves, and a loud systolic-diastolic murmur with thrill over the entire heart, and wide transmission of the systolic component. The roentgenogram showed "aortic" configuration of the heart, while cardiac catheterization disclosed a systolic gradient of 86 mm. across the pulmonary valve, with increased oxygen saturation in this location. Operation disclosed an abnormal coronary artery having the thickness of a finger, originating in a dilated sinus of Valsalva, showing a meandering course on the anterior heart wall, and terminating in the lumen of the right ventricle immediately beneath the pulmonary valves. The valvular pulmonic stenosis that was found to be present was corrected, but a defect in the ventricular septum proved too large to be repaired. Attempted occlusion of the aberrant aneurysmal coronary artery resulted in immediate cardiac arrest, as a small branch of this artery supplied the ventricular septum. After 4 attempts an idioventricular rhythm developed, and the operation could be completed. After 10 weeks the child was discharged greatly improved. No instance of the aberrant coronary artery described in this paper has been previously published.

LEPESCHKIN

Uchstein, J.: On Ebstein's Anomaly of the Tricuspid Valve. Arch. Kreislaufforsch. **26**: 282 (July), 1957.

On the basis of 3 personal cases and a review of the literature, 4 morphologic groups are differentiated. In the first group (8 cases) the anterior and posterior cusps originated at the anulus fibrosus but reached nearly to the ventricular apex; the underlying ventricular wall was abeculated and only the septal wall was smooth. In the second group (23 cases) the posterior cusp and the posterior part of the medial cusp originated midway toward the ventricular apex; in the third group (11 cases) the entire posterior wall was smooth and atrialized, while in group 4 (6 cases) the entire ventricle except a small portion near the pulmonary ostium was atrialized. The teratogenetic period for this anomaly is probably in the 15 to 20 mm. embryonic phase; this period is presumably latest in group 1 and earliest in group 4. The atrophy of the ventricular wall and the persistence of the foramen ovale are considered to be secondary effects of the valvular anomaly. Patients who lived to be 60, and presumably had only slight right atrial hypertension, had a closed foramen. Of the 72 patients with electrocardiograms, 53 showed right bundle-branch block (usually with low R wave in V_1-V_4), 32 peaked P waves and 16 prolonged P-R intervals. A Wolff-Parkinson-White pattern was found in 3; an accessory A-V connection was found in 1 of these, and also in 1 patient who did not show the pattern.

LEPESCHKIN

CORONARY ARTERY DISEASE

Losner, S., Volk, B. W., and Aronson, S. M.: Diagnostic Aids in Acute Myocardial Infarction: Clinical and Experimental. Am. Heart J. **54**: 225 (Aug.), 1957.

The present study reports the results and evaluation of serial determinations of plasma fibrinogen, serum glutamic-oxaloacetic transaminase, serum aldolase, the C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) in patients with acute myocardial insufficiency as well as in dogs with ligation of the left anterior coronary artery at various levels. With acute myocardial infarction the serum enzymes were observed to reach their peak concentration within 1 to 2 days after onset of symptoms and to return to normal 3 or 4 days later and the maximum fibrinogen concentration was found on the second or third day after coronary occlusion with return to normal levels in 2 or 3 weeks. The maximum blood level of these 3 blood constituents reflected the gravity of the disease and recurrent elevations during the stage of convalescence indicated extension of the area of infarction. The fibrinogen level also reflected a protracted clinical course and indicated such complications as intercurrent pericarditis, heart failure, or pulmonary embolization. The ESR and CRP also attained abnormal values in acute coronary occlusion, but were not found to reflect the severity nor the duration of the disease. In patients with coronary insufficiency or subendocardial necrosis the serum enzymes and fibrinogen concentration remained within normal limits or occasionally were only moderately elevated, but the ESR frequently was considerably elevated. In dogs with experimentally produced myocardial infarction the enzymes reached their peak levels within 24 hours and the fibrinogen within 2 days after operation. A semiquantitative relationship was observed between the extent of myocardial infarction and the maximum concentration of these blood constituents.

SAGALL

Wroblewski, F.: Clinical Significance of Serum Enzyme Alterations Associated with Myocardial Infarction. Am. Heart J. **54**: 219 (Aug.), 1957.

The author summarizes in this report the clinical significance of the alteration of serum glutamic-oxaloacetic transaminase (SGO-T) and serum lactic dehydrogenase (SLD) associated with myocardial infarction. From 6 to 12 hours following the onset of myocardial infarction there is a rise of 2 to 10 times the activity of these serum enzymes with a maximum elevation within 24 to 48 hours. The peak rise is proportional to the extent of myocardial tissue necrosis. The rise in SGO-T and SLD activity is not influenced by, nor correlated with, shock, blood pressure, heart failure, location of the infarction, anticoagulation, digitalis, quinidine, age, sex, color, body temperature, sedimentation rate, leukocyte count, or urinary output. Myocardial ischemia in the presence of confirmatory electrocardiographic changes without histologic evidence of necrosis does not result in significant elevation of enzyme activity. Although these serum enzymes may be altered in several other specific clinical situations, the serial and quantitative serum enzyme changes observed with acute myocardial infarction are not seen. In the presence of equivocal electrocardiographic findings or in tracings where the classical patterns of myocardial infarction are obscured by other abnormalities, the rise in SGO-T and SLD activity in a clinical setting suggestive of infarction is an especially helpful diagnostic tool.

SAGALL

Vastesaeger, M. M., Van der Straeten, P. P., Friart, J., Candaele, G., Ghys, A., and Bernard, R. M.: Anastomoses between Coronary Arteries Demonstrable by Postmortal Coronography. Acta cardiol. **12**: 365 (Fasc. 4), 1957.

The occurrence of anastomoses between coronary arteries in various animals and in fetal and adult human hearts was systematically studied with the help of a perfusion technic and by radiography following lipodol injection. Anastomoses could be demonstrated with variable frequency in the hearts of calves, pigs, sheep, horses, and dogs. The diameter of the anastomoses varied from one species to the other but also in the same species. Arteriolar anastomoses were noted in 6 out of 7 hearts of human fetuses and newborns. In 120 normal and diseased adult human hearts anastomoses were found in 80 per cent; and in 7.5 per cent of diameters up to 1 mm. The studied material failed to reveal a higher frequency of intercoronary communications in patients with coronary disease when compared with normal hearts. On the basis of these findings the authors concluded that anatomically intercoronary anastomoses are congenital and their occurrence has no relation to age or an occlusive coronary lesion. Arteriosclerotic occlusions, while unable to create new intercoronary communications may cause functional hypertrophy of pre-existent anastomotic vessels.

PICK

CONGESTIVE HEART FAILURE

Di Guiseppe, F.: A Clinical Study with Acetyldigitoxin, a New Digitalis Drug, for the Treatment of Congestive Heart Failure. Acta cardiol. **12**: 229 (March), 1957.

Thirty-eight patients with congestive heart failure due to various types of heart disease were treated by oral administration of acetyldigitoxin. In some patients an initial dose of 2.5 mg. was divided over 3 days and maintained by 0.25 to 0.3 mg. per day; side reactions were present in 25 per cent. In another group in which the initial dose was 2.2 to 2.6 mg. and the maintenance dose 0.15 to 0.2 mg. side reactions occurred in only 15 per cent and were less severe. In both groups they consisted in gastrointestinal disorders and disappeared 1 to 2 days after discontinuation of the drug. Ectopic impulse formation was never induced even with the higher doses and only exceptionally toxic effects appeared before the therapeutic ones. The latter occurred promptly, 16 to 18 hours after the first dose and the average dissipation time was 7 to 8 days. Thus, acetyldigitoxin had a more rapid action when compared with digitoxin, and a more persistent action when compared with lanata preparations. Acetyldigitoxin seems particularly indicated for the management of ambulatory patients with congestive heart failure.

PICK

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Henry, E. I., Schack, J. A., and Hoffman, I.: Significance of the Relation of QRS and T Waves in Bundle Branch Block: A Useful Electrocardiographic Sign. Am. Heart. J. **54**: 407 (Sept.), 1957.

In 22 of 415 instances of bundle-branch block the spatial angle formed by the terminal 0.04 second of QRS and the mean T vector (F04-T angle) was found to be 100 degrees or less. Of these cases 16 were right bundle-branch block, 5 left bundle-branch block, and 1 of an indeterminate type. Twenty of the 22 patients had obvious severe cardiac disease and 5 died of their heart disease. The finding of a narrow F04-T angle in bundle-branch block would appear to indicate the presence of severe organic heart disease. Thus, the determination of the F04-T angle may prove to be a valuable diagnostic sign especially in the evaluation of right bundle-branch block.

SAGALL

Gallavardin, L., and Delahaye, J. P: Pre- and Postoperative phonocardiography in Mitral Stenosis. Cardiologia **30**: 90 (Feb.), 1957.

In 18 patients with mitral stenosis acoustic phenomena were recorded before and following commissurotomy. Accentuation of the first heart sound was present in 12 and absent in 6 patients having a rigid or calcified mitral ostium or mitral regurgitation. A prolongation of the interval between the Q wave of the electrocardiogram and the onset of the first heart sound to 0.09 second or more was found in 7 patients with a very small mitral ostium and only in 1 patient with a relatively wide opening. This interval diminished in all following surgery. An opening snap succeeding after 0.07 second or less the second sound was found in 15 patients, disappeared postoperatively in 8, while in the other, its distance to the second sound became longer (0.84 second in the average). A diastolic rumble of variable intensity was recorded in 15 patients and disappeared practically in all after surgery. An apical systolic murmur of moderate intensity occurred in 6 patients, in 4 attributable to mitral

gurgitation found at operation and became ightly accentuated after the intervention.

PICK

onoso, E., Wachtel, F., and Grishman, A.: Polarity of the ST Vector. Am. J. Physiol. **189**: 219 (May), 1957.

Potassium chloride was applied to the epicardium to produce injury currents. Results obtained by a string galvanometer and a condenser coupled amplifier electrocardiograph were different. A string will remain deflected by a direct current as long as it flows. Condenser coupled amplifier machines indicate the same current voltage only for a brief period. Anterior wall injury depresses the base line, T-P, and P-R intervals. The S-T take off is isoelectric.

OPPENHEIMER

Gerard, R., Gras, A., and Benyamine, R.: Complications during Catheterization of the Coronary Sinus and Veins. Arch. mal. coeur **50**: 304 (April), 1957.

Of 350 consecutive cardiac catheterizations in mitral stenosis, 1 ended in death due to perforation of the coronary vein. At the moment of perforation the patient felt retrosternal pain, and a sample from the catheter disclosed a yellow liquid. At this time the catheter in the frontal view seemed to have the normal position in the pulmonary artery, with the tip directed upward. The electrocardiogram showed atrial flutter-fibrillation with right bundle-branch block and elevation of the S-T segment, while the pressure curve showed the same configuration as in the right ventricle. The patient died in shock 12 hours after catheterization. Of 12 catheterizations where the catheter entered the coronary vein the pressure curve showed an atrial type when the tip was near the coronary sinus, but a ventricular type in the 3 instances where it was blocked in a more peripheral vein; in these patients the absolute value of the pressure was at least twice as great in the right ventricle. A curve of ventricular configuration but variable amplitude is therefore a good sign that the catheter is in the coronary vein.

LEPESCHKIN

Wenger, R., Bhatia, B., and Hörtnagl, W: Atrial Fibrillation and Fibrillo-Flutter. Direct and Semidirect Leads in Human Hearts. III. Communication. Ztschr. Kreislaufforsch **46**: 345 (May), 1957.

In 20 patients with atrial fibrillation or impure flutter in the standard limb and precordial leads, intracardiac leads from parts of the right atrium or esophageal leads in contact with the left atrium may show pure flutter waves with sharp intrinsic deflections. In most patients the configuration of lead V_1 was similar to that of direct leads from the right atrium, but in a few patients flutter waves were absent in the former and present in the latter. The presence of intrinsic atrial deflections only in small regions of the right atrium would speak against the interpretation of flutter through circus movement around the great veins. In some patients with atrial fibrillation rhythmic activity at different rates was found in different regions of the right atrium, and this would favor the presence of several ectopic foci in this condition.

LEPESCHKIN

Pescador, L., de Prados, B. M., Otero, V. G., and Sainz, V.: Tomo-vectorcardiography. Arch. mal. coeur **50**: 266 (March), 1957.

Using the cube system of Duchosal and Sulzer (electrode location on the right side and the back), the horizontal plane vectorcardiogram was registered at 8 different levels of the thorax, each level corresponding to a different "section" through the electric field of the heart. The levels near the middle of the heart have higher voltage than in more peripheral regions. While differences in the angle of QRS between different sections are relatively slight in normal persons, in those with right ventricular hypertrophy they may reach 90°. These differences concern primarily the terminal portion of the QRS loop, while the initial portion remains stable. The sagittal plane vectorcardiograms can also be subdivided into 8 sections while in the frontal plane only 3 sections can be made. Wire models of the QRS loops in the 19 sections can be combined into 1 solid.

LEPESCHKIN

Erickson, R. V., Scher, A. M., and Becker, R. A.: Ventricular Excitation in Experimental Bundle-Branch Block. Circulation Research **5**: 5 (Jan.), 1957.

After experimental bundle-branch block in anesthetized dogs, the wave of excitation was observed to spread uniformly from the contralateral ventricle across the septum to the free wall of the homolateral ventricle. Changes in septal and mural depolarization contribute to QRS changes. Incomplete bundle-branch block appears most satisfactorily explained as caused by damage to the main bundle branch, rather than by interference with the endocardial or myocardial phases of induction.

AVIADO

Grabner, G., and Kaindl, F.: Statistical investigations of Spontaneous Variations of Basic Hemodynamic Basic Values in Cardiac Catheterization. Cardiologia **30**: 307 (May), 1957.

A critical investigation is presented concerning the exactness of hemodynamic data determined by cardiac catheterization. Among 65 patients including normal individuals and patients with various types of heart disease all catheterized under "basal conditions," statistically significant differences were found in multiple pressure readings in the pulmonary and systemic circulation, and in double determinations of the oxygen consumption and oxygen saturation of venous and arterial blood samples. Accordingly, inconsistent values were obtained in repeated calculations of cardiac output, of the work of the 2 ventricles and of the resistance in the 2 circulations. The authors, therefore, conclude that hemodynamic data arrived at by cardiac catheterization are merely an expression of transient conditions which, without known cause, may undergo considerable and apparently spontaneous variations exceeding the ranges of errors inherent in the method. In the evaluation of individual figures, much stricter criteria are necessary than applied in usual practice.

PICK

ENDOCARDITIS, MYOCARDITIS, PERICARDITIS

Kaipainen, W. J., and Seppälä, K.: Positive Wassermann and Kahn Tests in Endocarditis Lenta. Scandinav. J. Clin. & Lab. Invest. **9**: 144 (April), 1957.

Wassermann complement-fixation, cholesterine Wassermann, Kahn flocculation and occasionally sitolipin serologic tests were performed, frequently repeatedly, in 221 patients having subacute bacterial endocarditis in Helsinki. In 11 of these 1 or more positive reactions were encountered in association with other clinical evidence suggesting the presence of syphilis. This 5 per cent incidence of possible syphilis was nearly twice that of the over-all hospital incidence of syphilis. However, in only 1 instance was the infection proved to occur on a syphilitic valve. In 50 patients 1 or more positive reactions (most commonly in the Kahn test) were found in the absence of other evidence of syphilis, and it was suggested that knowledge of this nonspecific reaction incidence of 23 per cent might be of some help in making the diagnosis of endocarditis lenta.

ROGERS

Papadopol, S., Ioachim, H.: Histopathologic Aspects of 113 Auricular Biopsies Carried Out during Mitral Commissurotomy. Considerations on Latent Forms of Rheumatic Disease. Arch mal coeur **50**: 205 (March), 1957.

Subacute rheumatic endocarditis with Aschoff's nodules was found in 26.5 per cent, subacute endocarditis with lymphocyte infiltration in 6. per cent, and chronic sclerosing endocarditis in 67.2 per cent. There was no relation between the presence of Aschoff's bodies and the clinical or laboratory signs of acute rheumatic disease the interval since the last attack, or the appearance of the postcommissurotomy syndrome.

LEPESCHKIN

HYPERTENSION

Tobian, L., and Redleaf, P. D.: Effect of Hypertension on Arterial Wall Electrolytes during Desoxycorticosterone Administration. Am. J Physiol. **189**: 451 (June), 1957.

A desoxycorticosterone acetate (DCA) and salt regime was associated with increased sodium and potassium content of aortic walls in hypertensive rats. DCA and sodium restriction did not produce hypertension. In these animals the chemistry of the aortic wall was not changed.

OPPENHEIMER

PHARMACOLOGY

Delga, J., and Hazard, R.: Effect of Chlorpromazine on Various Actions of Adrenalin and Noradrenalin in the Dog. Arch. Int. Pharmacodyn. **109**: 446 (Feb.), 1957.

The authors studied the effect of chlorpromazine on the action of epinephrine and norepinephrine on blood pressure, blood sugar, and blood potassium. The experiments were performed on 12 dogs anesthetized with chloralose. Atropinisation of the animals before the experiments did not change the results. If chlorpromazine was given in doses that caused a fall in blood pressure following injection of epinephrine (0.6 to 4 mg. per Kg.) it prevented the hyperkalemia caused by epinephrine or even caused a fall of the blood potassium; however, it never modified the hyperglycemia caused by epinephrine, even if very large doses were given. Chlorpromazine diminished the hypertension caused by norepinephrine but did not cause a fall of the blood pressure. The hyperkalemia following injection of norepinephrine was easily suppressed.

SCHERF

Schmitt, H.: Dissociation by Phenotolamine of the Effects of Chemical Mediators (Adrenalin and Noradrenalin) and of the Actions Induced by Sympathetic Stimulation. Arch. Int. Pharmacodyn. **109**: 271 (Feb.), 1957.

Because of contradictory statements in the lit-

erature the author investigated the effect of phentolamine (Regitine) on the hypertensive action of stimulation of the peripheral end of the splanchnic nerve and the central end of the vagus nerve of the dog. Furthermore, the action of Regitine on the effect of faradic stimulation of the cervical sympathetic chain on the nictating membrane of the cat was examined. The dogs were anesthetized with chloralose, the cats with phenobarbital. The authors found that Regitine was a powerful adrenolytic substance; its noradrenolytic effect was less intense. In small doses Regitine potentiated the action of sympathetic stimulation. The vasomotor effect of faradic stimulation of the central end of the vagus was slightly augmented by Regitine. In small doses Regitine diminished the contraction of the nictitating membrane provoked by epinephrine and norepinephrine but it sensitized the membrane to the effect of nervous stimulation. The author points out that these results are not compatible with the present theory of humoral transmission of sympathetic impulses.

SCHERF

Schmitt, H.: Adrenolytic, Noradrenolytic and Sympathicolytic Action of Dibenzyline. Arch. Int. Pharmacodyn. **109**: 263 (Feb.), 1957.

The effects of dibenzyline on the action of epinephrine, norepinephrine and stimulation of the sympathetic nerves were investigated on cats and dogs. The animals were anesthetized with chloralose. The arterial blood pressure was registered from the femoral artery with a Ludwig mercury manometer. It was found that dibenzyline (1 to 10 mg. per Kg. intravenously in the dog) caused an inversion of the hypertensive action of epinephrine lasting for 8 to 9 hours. The hypertensive action of norepinephrine, however, was reduced only by 50 per cent. The rise of blood pressure after faradic stimulation of the peripheral end of the splanchnic nerve was not diminished. Dibenzyline diminished the rise of blood pressure produced by occlusion of both carotid arteries readily. Dibenzyline in the dose of 1 mg. per Kg. diminished considerably or even suppressed the contraction of the nictitating membrane of the cat, produced by epinephrine. It was concluded that dibenzyline was a powerful adrenolytic drug; it had less noradrenolytic action. Its activity as a sympathicolytic drug was the weakest. The substance also possessed an inhibiting action on the vasomotor centers.

SCHERF

Taquini, A. C., Roncoroni, A. J., Aramendia, P., and Ros, A. M.: Sensitivity of Respiratory Center to Carbon Dioxide in Emphysema and Cor Pulmonale: Effects of Carbonic Anhydrase Inhibition. Am. Heart J. **54**: 319 (Sept.), 1957.

The authors report in detail the results of a study of pulmonary ventilation and blood gases in normal subjects and patients with chronic cor pulmonale secondary to pulmonary emphysema in acute or chronic respiratory acidosis. The sensitivity of the respiratory center to carbon dioxide was evaluated by the change in ventilation induced by breathing carbon dioxide in air that brings about an acute increase in arterial carbon dioxide. An analysis was made of the factors responsible for this response and the modifications that could be exerted on it by the pharmacologic depletion of blood bicarbonates by means of acetazoleamide. It is concluded that acetazoleamide should be used cautiously in patients in acute respiratory acidosis since, if hyperventilation is not produced, it will result in a more severe acidosis. In chronic respiratory acidosis acetazoleamide seemed a valuable adjunct to the usual therapy.

SAGALL

Vitenshteinas, G. A.: Certain peculiarities in the Action of Atropine on the Heart. Klin. Med. **35**: 48 (May), 1957.

Subcutaneous injection of 1 mg. of atropine caused a paradoxical decrease of heart rate in about one third of 50 patients. In 1 patient atrioventricular nodal rhythm at a higher rate appeared. In 1 patient nodal rhythm accelerated at first, and then was transformed into sinus rhythm. One patient with angina pectoris had normal T waves at rest and after exercise, but developed precordial pain and inverted T waves after atropine.

LEPESCHKIN

METABOLIC EFFECTS ON CIRCULATION

Schaub, F.: Cardiac Alterations in Myxedema and Simple Hypothyroidism. Cardiologia **30**: 185 (March), 1957.

Cardiovascular findings were reviewed in 59 patients with myxedema or hypothyroidism, 18 to 79 years of age and with various etiologies. The leading symptom was dyspnea in myxedema and functional complaints in hypothyroidism. In one third of all patients the heart sounds were distant. Roentgenologically the heart was enlarged with feeble contractions in all myxedematous and in one fourth of the hypothyroid patients. One fourth of the former and one half of the latter did not have bradycardia. Hypertension was noted in the same percentage. One third of the myxedematous patients had evidence of pericardial effusion. Forty-six of the 59 pa-

tients revealed electrocardiographic abnormalities consisting in flattening or inversion of T waves, and small P waves. Low voltage, however, was found in only 10. Atrioventricular conduction delay was rare, but a right ventricular conduction disturbance was diagnosed in 26. In 22 the response to specific therapy could be followed. The cardiovascular findings became normal in 5 and improved in 13.

PICK

PHYSICAL SIGNS

Contro, S.: Ventricular Gallop in Mitral Stenosis. Its Mechanism and Significance. Am. Heart J. **54**: 246 (Aug.), 1957.

In 84 cases of mitral stenosis studied for the occurrence of true ventricular gallop, 5 cases of this type of triple rhythm were discovered and proved by simultaneous phonocardiograms, apex cardiograms, and jugular tracings. Four of these patients had associated tricuspid insufficiency and 1 had pure mitral insufficiency without stenosis. The mechanism of this rhythm and its distinction from other forms of triple rhythm are discussed. The author concludes that the discovery of a ventricular gallop rhythm in patients with mitral stenosis should alert one to the likelihood of the existence of other valvular abnormalities.

SAGALL

PHYSIOLOGY

Burn, J. H., Gunning, A. J., and Walker, J. M.: Effects of Noradrenaline and Adrenaline on the Atrial rhythm in the Heart-Lung Preparation. J. Physiol. **137**: 141 (June 18), 1957.

A standard heart-lung preparation was set up using heparinized blood. Epinephrine and norepinephrine were infused into the tube carrying the blood from the venous reservoir to the superior vena cava. Electric stimulation was supplied to the tip of the right atrium by electrodes. The right atrium was stimulated at increasing rates to determine the maximum rate at which all atrial beats were transmitted to the ventricles. Stimulation was continued at higher rates to determine what rate would cause a fall in ventricular rate until it became half the atrial rate. Epinephrine and norepinephrine were then infused into the cannula; the same type of stimulation was carried out. Infusion of epinephrine and norepinephrine raised the maximum rate of stimulation permissible and raised the rate at which stimulation could be maintained until the ventricular rate fell to half the atrial rate. Stimulation at very high rates (750 per minute for 2 minutes) was carried out during the infusion of epinephrine and later norepinephrine. No predicted effect of changing rhythm could be observed. When acetylcholine was injected, atrial flutter occurred. The addition of eserine to the experimental set up, followed by the infusion of epinephrine or norepinephrine caused no change in rhythm. When fibrillation had been produced by stimulation after the infusion of acetylcholine, the addition of epinephrine did not abolish this. The authors' ideas are advanced to explain these phenomenon. It is felt that the action is due to an increase in the duration of the atrial action potential caused by epinephrine.

HARVEY

Fowler, N. O., Duchesne, E. R., and Franch, R. H.: Hemodynamic Effects of Levarterenol Infusion during Inducted Pulmonary Stenosis. J. Pharmacol. & Exper. Therap. **120**: 115 (June), 1957.

Infusions of levarterenol (3 to 7.7 mg. per Kg. per minute) in anesthetized dogs with pulmonary artery constriction caused an increase in cardiac output, accompanied by cardiac acceleration and premature ventricular contractions. The difference between such results and those reported by Goldberg and co-worker in man (no increase in output) may be due to the following factors: species difference; modifying action of anesthesia; and larger dose used in dogs.

AVIADO

Page, I. H., Salmoiraghi, G. C., and McCubbin, J. W.: Cardiovascular Reactivity after Hepatectomy. Am. J. Physiol. **188**: 395 (Feb.), 1957.

Hepatectomy had little effect upon blood pressure responses to drugs in most cases. Reactions to drugs and reflexes were approximately normal in the perfused hind leg of these animals. In a smaller number of experiments responses to drugs were reduced. In these latter cases the depressor action of tetraethylammonium chloride was increased and serotonin became depressor. These last findings are a sign of increased neurogenic vasoconstriction. Hepatectomy did not increase responses to drugs concerned with blood vessels.

OPPENHEIMER

Kaufmann, G.: Circulation Times and Blood Distribution during Exercise. Cardiologia **30**: 102 (Feb.), 1957.

Cardiac output per minute, circulating blood volume, and circulation times were determined according to Hamilton's dye-dilution methods in 7 normal men at rest and following graduated exercise on a bicycle ergostat. Considering the over-all circulation, a good correlation was found

·tween the degree of work and the reduction of ıe average circulation times or of the ratio of ıe circulating blood volume to the cardiac out- ut, and the degree of work performed. Differ- ıtiation of circulation times for the segments ıeasured revealed that reduction was minor be- ween cubital veins and the ear as well as in the ·gment of lung capillaries to ear. Correspond- ıgly, an augmentation of the intrathoracic blood olume was found in 4 among 6 cases. This sug- ests that with normal circulation the blood sup- ly to the lungs is increased by exercise in most nstances.

PICK

Lüthy, E., Jeker, K., and Stucki, P.: Circulatory Studies during Hyperventilation. Cardiologia **30**: 139 (Feb.), 1957.

Alterations of venous return to the heart oc- curring with hyperventilation were investigated with the help of pressure recordings in the right atrium, in the subdiaphragmatic portion of the inferior vena cava, in the stomach, the esopha- gus, and the peritoneal cavity. It could be shown that hyperventilation reduced venous flow in nor- mal persons by some blocking mechanism devel- oping at the level of the diaphragm. This phe- nomenon was absent in patients with right heart failure but could be found during ordinary res- piration in patients with pulmonary emphysema.

PICK

Deldin, D. W., Rector, F. C., Jr., and Teng, H. C.: Effects of Prolonged Administration of Diamox of Excretion of Acid and Carbonic Anhydrase and Glutaminase Activities in the Kidney. Am. J. Physiol. **189**: 551 (June), 1957.

Acute and chronic effects of Diamox are simi- lar when inhibition of renal carbonic anhydrase is the criterion. Rats receiving Diamox in a chronic fashion were observed to have an alkaline urine, low titratable acid and high bicarbonate excretion. These findings depended on sodium Diamox load rather than carbonic anhydrase in- hibition. The renal glutaminase enzyme system was activated by chronic use of Diamox. As a result there was an increase of ammonia in an alkaline urine. If sodium was withheld, the ef- fect of Diamox on glutaminase was increased. Long-continued administration of Diamox was observed to be associated with an increase in se- rum sodium.

OPPENHEIMER

O'Meara, M. P., Birkenfeld, L. W., Gotch, F. A., and Edelman, I. S.: The Equilibration of Radiosodium (Na^{24}), Radiopotassium (K^{42}), and Deuterium Oxide (D_2O) in Hydropic Human Subjects. J. Clin. Invest. **36**: 784 (June), 1957.

In edematous patients equilibration of radio- sodium with readily exchangeable sodium re- quires at least 24 hours. In the case of radio- potassium the time required for equilibrium was twice as long as for sodium. However, deuter- ium oxide reached equilibrium in 6 hours.

OPPENHEIMER

Sullivan, B. J., and Towle, L. B.: Vascular Responses to Local Cold Injury. Am. J. Physiol. **189**: 498 (June), 1957.

The test object was the hamster cheek pouch. Vascular responses were proportional to time of exposure to cold. When exposed to freezing for 30 seconds, blood flow stopped in the area of ex- posure. Arteriolar constriction was not ob- served in this area, but was very definite in ad- jacent tissues. Following a thaw, the blood flow increased and many emboli of platelets were seen to originate from the previously frozen site. Sometimes adjacent vessels were the site of thrombus formation. Later flow decreased and came to a halt. Stasis began in veins and all types of vessels were in turn dilated by packed blood cells. The stasis depended on hemoconcen- tration.

OPPENHEIMER

Sullivan, B. J., and LeBlanc, M. F.: Effect of Inositol and Rapid Rewarming on Extent of Tissue Damage due to Cold Injury. Am. J. Physiol. **189**: 501 (June), 1957.

Cold injury in hind legs of hamsters was pro- duced by exposure to pulverized dry ice. If legs were rewarmed rapidly there was more edema, but less tissue necrosis. In controls that were not rewarmed, inositol increased edema with de- creased loss of tissue. Rapid rewarming and inositol were synergistic.

OPPENHEIMER

PULMONARY DISEASES

Daley, R.: The Autonomic Nervous System in Its Relation to Some Forms of Heart and Lung Disease. II. Lung Disease. Brit. M. J. **2**:249 (Aug. 3), 1957.

In this article the author discusses the signi- ficance of the autonomic nerve supply to the lung vasculature. On the basis of clinical observa- tions and some animal experiments he shows that pulmonary embolism is not accompanied by gen- eralized pulmonary vasoconstriction; that pul- monary edema is a secondary phenomenon to changes in the systemic circulation but facili- tated by pre-existing disturbances of pulmonary hemodynamics; that the hypoxic reaction is a direct response of the smaller vessels of the pul-

monary circulation to blood unsaturated with oxygen; and that drugs known to influence the autonomic nervous system play little part in the vascular adjustments of the lung. He further points out that the lung vasculature is poorly endowed with sympathetic and parasympathetic nervous supply and the function of even this small supply is not clear.

SAGALL

Ferri, F., Rovati V. Panesi, M. Romanelli, R., and Righini, E.: The Influence of the Vegetative Nervous System on Experimental Pulmonary Arterial Hypertension. Acta cardiol. **12**: 269 (March), 1957.

The authors were able to produce consistently in open chest dogs pulmonary arterial hypertension by ligation of the pulmonary veins. The diastolic pressure rose to 100 per cent of its initial value, while the systolic pressure was modified to a lesser degree and the capillary pressure remained unchanged. This hypertension could be intensified by norepinephrine, abolished by hexamethonium or Regitine and was not influenced by atropinization or bilateral vagotomy. The authors conclude that the mechanism of this type of pulmonary hypertension is a neurogenic reflex mediated by receptors in the walls of the pulmonary veins. The experiments confirm the influence of the sympathetic system in the genesis of functional pulmonary arterial hypertension.

PICK

Rosenberg, H. S., and MacNamara, D. G.: Primary Pulmonary Hypertension. Pediatrics **20**: 408 (Sept.), 1957.

A pulmonary arterial pressure increase develops when the ventricular ejectile force is common to both the pulmonary and the systemic circulations, or when there is interference with the pulmonary venous blood flow, or when there is pulmonary vasculitis or embolism. Primary pulmonary hypertension is a name reserved for that situation where none of the above conditions appears to be the cause for the pulmonary hypertension. A 4-month-old white baby girl was admitted to the Children's Hospital with progressive dyspnea for 2 months, cough for 1 month, and cyanosis for 2 weeks. The physical examination revealed clear lungs but an increased diameter of the chest. A faint blowing systolic murmur was heard in the third and fourth interspace on the left. The second pulmonic sound was accentuated. Tachycardia was present. The liver was felt 3 cm. below the right costal margin. X-ray showed prominence of the right atrial and ventricular shadows. The electrocardiogram showed right axis deviation and right ventricular hypertrophy. The initial impression was primary pulmonary hypertension. Cardiac catheterization was performed revealing elevation of pressure in right ventricle and pulmonary artery. The patient died suddenly 2 days after the catheterization. At autopsy microscopic examination of the lungs showed striking thickening of the walls of the pulmonary vessels due to increase in size of the medial layer. There was no fibrosis or necrosis and no endothelial change. Good illustrations of the microscopic sections are presented.

HARVEY

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Johnson, B. B., Lieberman, A. H., and Mulrow P. J.: Aldosterone Excretion in Normal Subjects Depleted of Sodium and Potassium. J. Clin. Invest. **36**: 757 (June), 1957.

Aldosterone excretion was reduced by potassium restriction, but when sodium restriction was added, excretion increased to 6 times. If potassium was restored while sodium deprivation continued there was some additional increase in excretion of aldosterone.

OPPENHEIMER

Wagner, H. N., Jr.: The Influence of Autonomic Vasoregulatory Reflexes on the Rate of Sodium and Water Excretion in Man. J. Clin. Invest. **36**: 1319 (Sept.), 1957.

The patients studied had an unexplained hypofunction of the autonomic nervous system. The symptoms were low blood pressure, hypohydrosis, and impotence. These subjects were observed to have a marked increase in ability to excrete salt and solute-free water when isotonic salt solution was injected intravenously. There was a concomitant increase in glomerular filtration rate and an expansion of extracellular fluid. Vasopressin blocked the increase in excretion of solute-free water. Adrenal steroids, known to be sodium-retaining, did not prevent the increase in sodium excretion. If blood or extracellular fluid volume was rapidly increased or decreased, marked shifts in systemic arterial blood pressure were observed. It is suggested that these patients are unable to maintain circulatory homeostasis and hence are capable of rapid increases in glomerular filtration rate and salt excretion. It is further postulated that, in normal individuals, well-developed autonomic vasoregulatory reflexes act to maintain circulatory homeostasis and as a result rapid increases in glomerular filtration rate and excretion of excess salt are not observed.

OPPENHEIMER

Robinson, J. G., Edwards, J. E., Higgins, G. M., and Burchell, H. B.: Effect of Digitalis on Incidence of Myocardial Lesions in Potassium-Deficient Rats. Arch. Path. **64**: 228 (Aug.), 1957.

In a pathologic study of the myocardium of potassium-deficient rats, no relationship between the administration of digitalis and the incidence or appearance of lesions due to potassium deficiency could be demonstrated. Digitalis neither protected from nor added to the effects of such a deficiency in so far as the production of recognizable lesions was concerned. It was also concluded that digitalis did not exert any significant influence upon the potassium or sodium content of the heart. Myocardial lesions that could be definitely attributed to the influence of potassium deficiency were not found in any of 74 patients who died of idiopathic ulcerative colitis. Specific electrocardiographic changes that could be definitely attributed to the effects of either potassium or digitalis were not demonstrated in a small group of rats studied.

MAXWELL

Dieckmann, W. J., Potter, E. L., and McCartney, C. P.; Renal Biopsies from Patients with "Toxemia of Pregnancy." Am. J. Obst. & Gynec. **73**: 1 (Jan.), 1957.

Renal biopsies were obtained in 122 pregnant or recently pregnant patients over a 7-year period. Of these, 69 were transperitoneal at the time of cesarean section and 53 were percutaneous. The present report is concerned with the first 71 biopsies including 26 primiparous and 45 multiparous patients. The diagnoses on renal tissues were made without knowledge of the clinical condition. On histologic grounds, a mild change (1+) consisted of thickening of basement membrane, fibrillation of endothelial cells, and slight reduction of the capillary lumen. This was found in 1 eclamptic, 3 nephritic, 13 hypertensive, and 4 normal patients. The mild lesion occurred rarely in pre-eclampsia but was frequent in multiparous patients with hypertensive disease. A moderate or severe change (2+ or 3+) consisted of more advanced thickening of basement membrane, fibrils in endothelial cells and narrowing of glomerular capillaries. This change was present in all 11 primiparous patients with pre-eclampsia, in 2 of 3 with eclampsia, and in 5 of 7 with hypertensive disease. It was concluded that this lesion may occur in any type of toxemia of pregnancy and is most common in primiparous patients with pre-eclampsia. There was no evidence that permanent renal damage developed from the lesion. There was also no evidence that the grade 2 or 3 lesions were characteristic of pre-eclampsia, since they were observed in hypertensive patients. It may be assumed that the lesions are a secondary rather than a primary factor in toxemia of pregnancy.

SHUMAN

Kovacs, K., Kovacs, G. S., Kovacs, B. M., and Petri, G.: The Effect of Chlorpromazine on the Activity of the Antidiuretic Hormone. Arch. int. pharmacodyn. **109**: 1 (Jan.), 1957.

Previous investigations of the authors have shown that a "lytic cocktail" containing chlorpromazine prevented the antidiuretic effect of surgical stress. Therefore, the effect of chlorpromazine on the antidiuretic action of posterior pituitary extracts and on that of the antidiuretic hormone-mobilizing nicotine was studied. Moderate inhibition of the diuretic action in orally waterloaded rats was produced by nicotine or a posterior pituitary preparation. The effect of chlorpromazine on this antidiuretic action was studied on 304 male and female albino rats. The animals, treated with chlorpromazine (1.5 mg. per 100 Gm. of body weight) scarcely moved and hardly responded to external stimuli. Neither nicotine nor pituitary hormone changed this. The water-loaded controls developed a characteristic diuretic response. The above-mentioned dose of chlorpromazine did not alter the diuretic response. When larger doses were used, the results were not uniform. Nicotine caused a characteristic antidiuretic effect. If the above-mentioned dose of chlorpromazine were given besides nicotine a very pronounced antidiuretic effect was observed. The mechanism of this effect could not be determined.

SCHERF

Rahman, M. H., Frazier, L. E., Hughes, R. H., and Cannon P. R.: Electrolyte Imbalance and Intracellular Potassium-Sodium Exchange. Arch. Path. **63**: 154 (Feb.), 1957.

The feeding to growing rats of nutritionally adequate diets high in sodium chloride content but low in potassium led to markedly increased urinary excretion of potassium and the development of focal myocardial necrosis characteristic of potassium deficiency. Such lesions did not appear or were minimal in animals fed similar diets low in sodium chloride. The largest weight gains occurred in animals receiving normal amounts of potassium and sodium; and the smallest weight gain occurred in those animals receiving the highest sodium dietary content. Hypertension did not develop in any of the animals. These experiments support the view that ionic imbalance between sodium and potassium,

under conditions of excessive intakes of sodium, may lead to an intracellular displacement of potassium and a subsequent development of cardiac lesions indicative of potassium deficiency. The inference is that a preponderance of sodium ions within the cell may be the determinant of potassium displacement.

MAXWELL

Spinazzola, A. J. and Sherrod, T. R.: The Effects of Serotonin (5-Hydroxytryptamine) on Renal Hemodynamics. J. Pharmacol. & Exper. Therap. **119**: 114 (Jan.), 1957.

The most striking effect of serotonin on renal hemodynamics is its antidiuretic action. The threshold dose of 10 mg. per Kg. per minute (in dogs) results in a significant decrease in urine formation in the absence of any changes in glomerular filtration rate of blood pressure and with only an insignificant increase in renal plasma flow. This strongly suggests an action of this agent to increase the rate of water reabsorption by the renal tubules.

AVIADO

RHEUMATIC FEVER

McAfee, J. G., and Biondetti, P.: Roentgenologic Follow-Up on 150 Consecutive Mitral Commissurotomy Patients. Am. J. Roentgenol. **78**: 213 (Aug.), 1957.

Adequate roentgenologic data were available in 115 patients. Almost half of these had transient enlargement within the first 3 months after the operation, enlargement was persistent in from 1 to 5 years in 24 per cent; a decrease in size occurred in 22 per cent. In general, decreases in size correspond to the degree of clinical improvement. Increase in size occurred in 78 per cent of the patients clinically improved. Calcification of the mitral valve occurred in 43 per cent of patients with mitral insufficiency and in 10 per cent of patients with mitral stenosis. The incidence of giant left atria was about the same in both. In general, there was fairly good correlation between the grades of prominence of the pulmonary artery trunk, horizontal Kerley "B" lines, and demonstrable pulmonary hypertension during cardiac catheterization. The disappearance of the "B" lines often coincided with clinical improvement.

SCHWEDEL

Alexander, W. D., and Andrews, M. M.: Discrepancies in the Erythrocyte-Sedimentation Test in Rheumatic Fever. Lancet **2**: 240 (Feb. 2), 1957.

Poor reproducibility of results with all commonly employed methods is reported. The poor reproducibility is not confined to rheumatic fever.

MCKUSICK

Quinn, R. W.: The Response of Rheumatic and Non-Rheumatic Children to Streptolysin O Concentrate. J. Clin. Invest. **36**: 793 (June), 1957.

Streptolysin O concentrates were administered intramuscularly to 20 children with rheumatic fever. Nonrheumatic children were used as controls. Nonspecific antibody responses were not observed following administration of Streptolysin O. Rheumatic children had higher antistreptolysin O responses than did normal controls.

OPPENHEIMER

ROENTGENOLOGY

Muller, R. F., and Figley, M. M.: The Arteries of the Abdomen, Pelvis, and Thigh. I. Normal Roentgenographic Anatomy. II. Collateral Circulation in Obstructive Arterial Disease. Am. J. Roentgenol. **77**: 296 (Feb.), 1957.

The authors provide a descriptive account of the roentgenographic anatomy of the arteries of the abdomen and pelvis as visualized by means of translumbar aortography. Studies of the collateral circulation in 151 patients with arterial obstruction confirmed previous anatomic descriptions of collateral channels and did not disclose any new anastomoses. Collateral circulation may form from 1 of 3 sources: segmental and parietal arteries, visceral arteries, and opposing arteries. Segmental and parietal arteries include the intercostal, lumbar, inferior epigastric, and deep circumflex iliac arteries, usually with other segmental and parietal arteries on the same side of the body. Visceral arteries include the superior and inferior mesenteric arteries and their branches and the visceral branches of the hypogastric arteries, and supply blood to the lower extremities via the parietal branches of the hypogastric artery, and the obdurator, superior, and inferior gluteal arteries. Opposing arteries are the branches of the hypogastric artery, both visceral and parietal, which are capable of anastomosing with their fellows across the midline, and are observed principally in unilateral pelvic artery obstruction.

SCHWEDEL

Schwedel, J. B., Escher, D. W., Aaron, R. S., and Young, D.: The Roentgenologic Diagnosis of Pulmonary Hypertension in Mitral Stenosis. Am. Heart J. **53**: 163 (Feb.), 1957.

In an attempt to find a readily applicable method for determining the presence or absence of pulmonary hypertension, the chest x-rays of

05 patients with pure or significantly predominant mitral stenosis in whom pulmonary artery pressures had been measured directly by cardiac catheterization, or by direct puncture of the pulmonary artery at operation, were studied in regard to the width of the right descending pulmonary artery. The authors concluded that in such patients widths of 15 mm. or more are definitely associated with significant pulmonary hypertension, widths of 14 mm. indicate that significant pulmonary hypertension is most likely present and with widths below 14 mm. there is no certainty as to the existence of pulmonary hypertension. Also, no direct linear correlation was found between increased pulmonary artery widths and the degree of pulmonary hypertension.

SAGALL

Steinbach, H. L., Jergesen, F., Gilfillan, R. S., and Petrakis, N. L.: Osseus Phlebography. Surg., Gynec. & Obst. **104**: 215 (Feb.), 1957.

Heretofore, intraosseus injections of radiopaque media have been employed mainly in the tibia for the purpose of demonstrating the deep and superficial veins of the lower extremity. The authors describe additional uses of this technic delineating lesions affecting either intraosseous or extraosseus venous patterns. Examples of the former type are bone cysts and neoplasms, osteitis pubis, and fractures. Extraosseus lesions that may be demonstrated by phlebography via adjacent bones are intraspinal and mediastinal tumors. General anesthesia is usually required.

ROGERS

Johnson, J. B., Lawlah, J. W., McFadden, F., and Dyer, J. F., Jr.: Thoracic Aortography. Am. Heart J. **53**: 40 (Jan.), 1957.

The authors report a study of contrast visualization of the ascending and transverse aorta with a technic involving retrograde catheterization of the aorta through the femoral artery and the use of sodium and methylglucamine diacetylaminotriiodobenzoates (Renografin 76 per cent). In all, 86 injections were made in 18 patients without the need of general anesthesia and without serious reactions or complications. Study of this anatomic area previously by angiocardiography has not proved reliable. Also, the danger of brain damage following direct aortography has prevented large scale use of this method. Retrograde thoracic aortography, however, has made it possible to outline the root of the aorta, including the aortic valve, the aortic arch, and its branches, accurately as well as the remainder of the thoracic and abdominal aorta. This procedure has greatly improved the delineation of the vascular nature of masses associated with the root of the aorta, the aortic arch, and the brachiocephalic arteries. Other observations that may be made in certain instances with this method of study include visualization of the coronary, vertebral, and cerebral arteries and the obtaining of hemodynamic data of the left ventricle when the catheter tip has entered the cavity.

SAGALL

Crawford, E. S., Beall, A. C., Moyer, J. H., and DeBakey, M. E.: Complications of Aortography. Surg., Gynec. & Obst. **104**: 129 (Feb.), 1957.

Translumbar aortography has had a small though significant rate of complications. Mainly these are renal and spinal cord damage (each due to local action of contrast medium), hemorrhage (usually due to multiple punctures or to moving the patient while the needle is in place), thrombosis not of the aorta but of a branch, and embolism of a thrombus or an atheromatous plaque. These difficulties can usually be avoided by employing the following technic. The aorta should be pierced only once, well above its major abdominal branches, with a 17-gage thin-walled needle. Five milliliters of an organic iodide solution is injected and a preliminary roentgenogram is made to ascertain the position of the needle. Then 15 to 25 ml. of the iodide solution are injected manually to produce the aortograms. Aortography is not needed in most patients with abdominal aortic aneurysm or of total aortic occlusion.

ROGERS

Wilder, R. J., Moscovitz, H. L., and Ravitch, M. M.: Roentgen Contrast Diagnosis of Experimental Mitral and Aortic Insufficiency in Dogs by Transventricular Injection and Retrograde Catheterization. J. Thoracic Surg. **33**: 147 (Feb.), 1957.

The authors studied the safety and efficiency of direct cardioangiography and retrograde aortography in dogs. Some of the dogs had been subjected to the surgical production of mitral insufficiency, mitral stenosis, and aortic insufficiency. It was found that normal mitral and aortic valves prevented retrograde reflux of the contrast medium. Mitral insufficiency was clearly shown after injection of the left ventricle, when the contrast medium appeared in the left atrium. Aortic insufficiency resulted in reflux visualization of the left ventricle after injection into the ascending aorta. The combination of mitral stenosis and insufficiency was also demonstrable after injection into the left ventricle. The authors found that the retrograde aortographic technic was safer for left

ventricular injection than the direct puncture technic.

ENSELBERG

McAfee, J. G.: A Survey of Complications of Abdominal Aortography. Radiology **68**: 825 (June), 1957.

Thirty-seven deaths and 98 serious complications occurred in a survey series of 13,207 abdominal aortographies. The mortality rate was 0.28 per cent; serious morbidity in 0.74 per cent. Renal damage from the contrast medium was the most important complication, followed in order of frequency by neurologic, cardiovascular, and gastrointestinal morbidities and mortalities. Hemorrhage and general anesthesia occurred frequently enough to warrant serious consideration; respiratory morbidity occurred less often only than renal and neurologic causes.

SCHWEDEL

SURGERY AND CARDIOVASCULAR DISEASE

Mulcahy, R.: Mitral Valvotomy in Pregnancy. Acta cardiol. **12**: 349 (Fasc. 4), 1957.

Seven patients with pure mitral stenosis are reported who underwent mitral surgery at various stages of pregnancy. The feasability of the operation was demonstrated by the fact that all patients made an uneventful recovery and completed their pregnancy. The indications for commissurotomy during pregnancy are discussed. It is emphasized that the operation may constitute an important therapeutic procedure particularly in countries where termination of pregnancy and sterilization are not practiced. Under such circumstances mitral surgery will significantly contribute to the reduction of the mortality figures from heart disease.

PICK

Ricordeau, G., Coblentz, B., and Lenègre, J.: Arterial Embolism in Mitral Stenosis and Commissurotomy. Arch. mal. coeur **50**: 112 (Feb.), 1957.

Of 370 patients with mitral stenosis submitted to commissurotomy, 48 had previously had arterial emboli, and 17 of these had multiple emboli. In 12 of the 48, atrial thrombosis was found during the operation; all of them had atrial fibrillation. In 3 of these embolism occurred during the operation, whereas it occurred in only 3 of the 322 patients without previous embolization. In patients with previous emboli it is recommended to interpose 2 months of anticoagulant treatment between the last embolism and the operation, to flush the atrium and to clamp the carotid arteries temporarily. Non of the patients who had previously had embol developed them during a period averaging 1 months after the operation.

LEPESCHKIN

Bigelow, W. G., Heimbecker, R. O., and Trusle G.: The Practical Management of Cardiac Ar rest. Canad. M. A. J. **76**: 86 (Jan. 15), 195

Abrupt arrest of the circulation, occurrin in 34 of 600 heart operations, was due t ventricular fibrillation in 28 and to cardia arrest in 8. Prophylaxis (including avoidan of intraoperative hypoxia, hypotension, and u due cardiac trauma) was not always possibl Once circulatory arrest is diagnosed, effectiv treatment must be instituted within 4 minutes i permanent brain or heart damage is to be pr vented. First, an adequate airway is establishe and oxygen is administered. Forceful ventricula massage against the spine or sternum at a rat of 60 to 70 per minute is carried out usuall through a fourth left intercostal and pericardial incision. Response is gauged by systolic blood pressure rise to at least 70 mm. Hg. Cardiac ton may be augmented by injecting 1 to 5 ml. of 10 per cent calcium chloride or a 1:10,000 epinephrine solution into the left ventricular cavity. Most cases of cardiac standstill will respond to this treatment, while ventricular fibrillation usually requires in addition defibrillation by electric countershocks. When the spontaneous heart beat has resumed adequately for several minutes, the chest incision is closed with underwater drainage of the pericardium.

ROGERS

Gott, V. L., Gonzales, J. L., Zuhdi, M. N., Varco, R. L., and Lillehei, C. W.: Retrograde Perfusion of the Coronary Sinus for Direct Vision Aortic Surgery. Surg. Gynec. & Obst. **104**: 319 (March), 1957.

Maintenance of the circulation of dogs by means of a pump oxygenator alone for periods of 15 minutes resulted in the development of ventricular fibrillation in all, and death in 90 per cent. The additional retrograde perfusion of the coronary sinus with blood from the pump oxygenator preserved heart action satisfactorily in 15 of 16 dogs for periods up to 20 minutes, although 4 of these animals developed ventricular fibrillation after the reestablishment of normal coronary blood flow. Some physiologic, electrocardiographic, and metabolic data from these studies are presented.

Seven patients are described having direct-vision left heart surgery for as long as 16 minutes using the latter technic for circulatory

support. Successful results include the correction of aortic or subaortic stenosis, of combined rheumatic aortic and mitral valvular lesions, and of a sinus of Valsalva rupture into the right ventricle. Three deaths occurred postoperatively. In all patients this method of circulatory maintenance appeared to protect the myocardium against hypoxia and coronary air embolism.

ROGERS

Cahue, A., and Pick, A.: Acute Alterations of the Electrocardiogram Following Thoracic Surgery. Dis. Chest **31**: 14 (Jan.), 1957.

Postoperative arrhythmias and pericarditis were studied in 55 patients who had established normal sinus rhythm prior to thoracic or cardiac surgery. Disturbances in rhythm developed in 20 instances, electrocardiographic evidence of pericarditis in 27, and questionable changes in 3. Concomitant arrhythmia and pericarditis occurred in 10. Atrial flutter or fibrillation was the most common arrhythmia encountered (75 per cent) regardless of type of surgery and was the only disturbance of rhythm occurring after mitral commissurotomy (7 of 13 patients). None of the 4 patients submitted to pulmonary valvulotomy developed arrhythmia. Among the 10 patients who underwent surgery for carcinoma of the esophagus, disturbances of rhythm were noted in 7, all of whom died within 1 to 22 days. Most of the disturbances of rhythm occurred within 5 days after operation; late onset, more than 10 days after surgery, suggested serious postoperative complications or reactivation of the rheumatic process. The most important factors in the development of postoperative atrial arrhythmia appeared to be the age of the patient and pre-existent disease of the atrial myocardium. Hypoxemia or vagal irritation may trigger the abnormal mechanism. Surgical pericarditis has an early onset and may follow the usual or an abbreviated electrocardiographic course. Alterations of the electrocardiogram attributable to pericarditis can be anticipated in any patient in whom the pericardial sac is opened.

MAXWELL

Kay, J. H., Dever, R., Gaertner, R. A., and Kaiser, G. C.: Treatment of Cardiac Arrest Occurring during Surgery. J. A. M. A. **163**: 165 (Jan. 19), 1957.

Cardiac arrest may occur during surgery in patients who have impairment of myocardial blood supply, chronic respiratory embarrassment, or overdosage of an anesthetic agent. Massive hemorrhage and the vaso vagal reflex may be factors. There are 2 forms of cardiac arrest: ventricular standstill or ventricular fibrillation. It is useful to differentiate these because the treatment is different. Many cases of ventricular standstill will respond to 1 or 2 minutes of cardiac massage alone. If this is not effective, 1 ml. of 1:1000 solution epinephrine hydrochloride is diluted with 9 ml. of saline solution and 2 or 3 ml. of this is injected into the left ventricular cavity while the heart is massaged. This injection may be repeated many times. In congenital heart disease, 2 to 4 ml. of a 10 per cent solution of calcium chloride may be effective. When a heart is in ventricular fibrillation the only consistently effective method of carrying out defibrillation is by electric means (using 130 volts for 0.25 second, or 220 volts for 0.10 second). The authors have not found isoproterenal hydrochloride, calcium gluconate, or barium chloride to be satisfactory cardiac stimulants.

KITCHELL

Ryan, E. P., Johnson, G., Jr., and Beal, J. M.: An Experimental Aortic Valve. Proc. Soc. Exper. Biol. & Med. **94**: 372 (Feb.), 1957.

The correction of aortic valvular insufficiency remains an unsolved problem. A method has been described for the experimental production of an aortic flutter valve in dogs. Evidence of competency of the valve had been obtained by means of direct arterial pressure recordings above and below the valve in association with avulsion of the cardiac aortic valve. The use of autogenous body tissues would be preferable to employment of plastic materials (Hufnagel valve) which have the potential danger of creating foreign reactions, erosion of vessel wall, dislodgement, and thrombosis. A major objection to the new method is the location of the valve distal to the coronary arteries. It is obvious that a longer period of observation is required to determine its effectiveness.

AVIADO

Dodrill, F. D., Marshall, N., Nyboer, J., Hughes, C. H., Derbyshire, A. J., and Stearns A. B.: The Use of the Heart-Lung Apparatus in Human Cardiac Surgery. J. Thoracic Surg. **33**: 60 (Jan.), 1957.

The authors present 2 innovations in extracorporeal circulation. The first consists of exchange transfusion, in which a portion of the patient's blood is removed and the patient maintained on donor's blood. At the end of the operation the used blood is washed out and the original blood returned to the patient. The rationale for this method is the observation that various hematologic and enzyme defects are common as a result of injury to the blood during extracorporeal circulation.

The second innovation is in suturing an aortic graft on to the side of the aorta, producing a large orifice through which arterialized blood can be returned to the system. This large orifice permits the maintenance of a normal or relatively normal blood pressure with preservation of the pulse pressure.

Observations in human subjects have shown that these technics result in maintenance of normal blood flows, arterial oxygen saturations, plasma carbon dioxide levels, pH of blood, blood platelets, and usually normal electroencephalograms. The authors have used these procedures in 6 patients (5 interventricular defects and 1 tetralogy of Fallot). The operative mortality was 50 per cent.

ENSELBERG

Wheelock, F. C., Jr., McKittrick, J. B., and Root, H. F.: Evaluation of the Transmetatarsal Amputation in Patients with Diabetes Mellitus. Surgery **41**: 184 (Feb.), 1957.

This report evaluates the immediate and long-term results in 433 transmetatarsal amputations in diabetic patients. Candidates for the operation were divided into 2 groups: group 1 consisted of patients with neuropathy and severe infection but with a good arterial circulation and group 2 consisted of patients with necrosis and arterial insufficiency. Follow-up studies on 57 group 1 patients showed that 22 died of causes unrelated to their feet. One was a postoperative death. Five late failures required higher amputation from 1 to 8 years after the initial operation. Forty-four of 47 patients (93.5 per cent) living for 3 years following amputation were doing well. Among those alive 5 years or more after amputation 31 of 34 (91.2 per cent) were doing well. Follow-up studies were obtained in 348 of 366 group 2 patients (95 per cent). At the time of the report 88 were alive and using the involved foot. There were 4 postoperative deaths and 134 died after leaving the hospital. One hundred and twenty of the operations failed eventually and 2 remained unhealed. At the end of 1 year, 218 of 317 patients (69 per cent) were living and doing well. At the end of 3 years, 156 of 255 (61 per cent) were doing well. After 5 years or more 87 of 174 (50 per cent) patients living were healed. Thirty seven patients had bilateral amputations on different admissions. It is concluded that in properly selected diabetic patients, transmetatarsal amputation has proved to be sufficiently successful to warrant its continued use.

BROTHERS

UNCOMMON FORMS OF HEART DISEASE

Pascuzzi, C. A., Parkin, T. W., Bruwer, A. J. and Edwards, J. E.: Cardiac Clinics, CXLVII. Hypertrophic Osteoarthropathy Associated with Primary Rhabdomyosarcoma of the Heart. Proc. Staff Meet., Mayo Clin. **32**: 30 (Jan.), 1957.

The authors describe a case in which a 25-year-old woman died of primary rhabdomyosarcoma of the heart. The prominent features of the illness were arthralgia, clubbing of the fingers, and periosteal proliferation of long bones. Angiocardiography and pericardial biopsy permitted the diagnosis of primary sarcoma of the heart to be made ante mortem. The serum mucoprotein was increased to twice the normal value. Wide-field irradiation therapy with cobalt^{60} was ineffective.

SIMON

Soulie, P., di Matteo, J., Abaza, A., Nouaille, J., and Thibert, M.: Familial Cardiomegaly. Arch. mal coeur **50**: 22 (Jan.), 1957.

A 22-year-old brother, a 13-year-old sister, and a 54-year-old uncle showed marked cardiac enlargement without signs of hypertension or valvular disease. The electrocardiogram showed incomplete left bundle-branch block with short P-R interval and resembled the Wolff-Parkinson-White pattern. Another brother died suddenly at the age of 20. Another patient not belonging to the family but showing the same signs is described. One of the patients died in congestive failure, and at autopsy normal coronary arteries and valves were found. All chambers of the heart, but especially the left ventricle, were hypertrophied, and the myocardium showed disseminated sclerosis with vacuolization of the fibers.

LEPESCHKIN

Averill, J. H., Randall, R. V., Joffe, E., and White, P. D.: Heart Disease of Unknown Cause in Siblings. Ann. Int. Med. **47**: 49 (July), 1957.

Ten cases of cardiac disease of unrecognized cause occurring in 5 pairs of siblings are reported in this paper. All succumbed to their illness and necropsies were obtained in 7 patients. Although the pathologic features varied from one patient to another, the clinical course was similar. Common features were progressive congestive heart failure frequently similar to that associated with constrictive pericarditis, cardiac arrhythmias, peripheral emboli, and enlargement of the heart often without significant murmurs. In 3 of the patients, the exclusion of constrictive pericarditis was made possible only after surgical exploration of the pericardium. From the pathologic view, endocardial fibroelastosis, myocardial hypertrophy, and myocardial fibrosis were the constant findings. The presence of cardiac disease

of unknown cause in these pairs of siblings suggests that the primary defect was possibly congenital. The frequent finding of endocardial fibroelastosis tends to support this view, inasmuch as this type of pathologic change in the heart is frequently considered to be the result of a developmental defect.

WENDKOS

VALVULAR HEART DISEASE

Harvey, W. P., Segal, J. P., and Hufnagel, C. A.: Unusual Clinical Features Associated with Severe Aortic Insufficiency. Ann. Int. Med. **47**: 27 (July), 1957.

A review of about 300 cases of severe aortic insufficiency has revealed a number of unusual clinical aspects that have not previously received the recognition that they deserve. Sudden death was most common in patients with previous ventricular extrasystoles, usually with more advanced cardiac disease, and was attributed to the development of ventricular fibrillation. Excessive perspiration was observed in a majority of patients with severe congestive failure. The intolerance to heat was sufficiently severe to suggest in many cases the presence of hyperthyroidism but studies failed to demonstrate any evidence of thyroid overactivity. Carotid arterial pain was frequently bilateral and was located over the carotid arteries. This commonly lasted 5 to 7 days and required narcotics for relief. Although presumably the pain was due to stretching of the carotid sheath, in some patients the vigorously pulsating carotid artery in the vicinity of inflamed tender lymph nodes, secondary to an upper respiratory infection, may have played an etiologic role. Abdominal pain was nonspecific and could simulate the pain of peptic ulcer, biliary tract disease, pancreatitis, or even renal colic. The abdominal discomfort appeared to differ from that associated with hepatic engorgement in congestive failure. The pain was probably secondary to the constant stretching of the wall of the abdominal aorta. Pounding sensations were generally described as a throbbing in the head and neck but at times the patient was literally aware of the entire body being jolted back and forth. This was particularly noticeable during periods of rest in bed and the patients generally wore loose-fitting collars to minimize the pounding sensation from the carotid arteries. Angina pectoris occurred in about 50 per cent of the patients and was not unusual in its manifestations except that it was predominantly present at night and was generally prolonged. It was common in association with severe aortic insufficiency regardless of whether the origin was rheumatic or syphilitic. Other unusual associations with aortic insufficiency were splashing sounds over the stomach, rheumatoid spondylitis, coarctation of the aorta, and the Marfan syndrome, the last being characterized by defects in the media of the ascending aorta, gracile habitus, high-arched palate, subluxation of the lens of the eyes, and unusual freedom of movement of the joints.

WENDKOS

Schilder, D. P., and Harvey, W. P.: Confusion of Tricuspid Incompetence with Mitral Insufficiency—A Pitfall in the Selection of Patients for Mitral Surgery. Am. Heart J. **54**: 352 (Sept.), 1957.

Five patients with severe mitral stenosis are presented. All of these patients were suspected initially of having significant mitral insufficiency because of a loud apical systolic murmur, but on careful evaluation the systolic murmur proved to be that of associated tricuspid valve incompetence. At surgery, severe mitral stenosis without insufficiency was discovered and operation was followed by uniformly good results. The authors point out that these patients are representative of an important group with mitral stenosis that is frequently denied the benefit of surgery because associated tricuspid incompetence masquerades as mitral insufficiency. Certain characteristics of the transmitted murmur of tricuspid incompetence may help in establishing the proper diagnosis. The murmur of tricuspid incompetence varies considerably in nature, frequently seems close to the ear, is heard best over the xiphoid area and along the lower left sternal border, characteristically is inconstant in appearance, varies in intensity, and becomes louder following exercise and deep inspiration (Carvallo's sign). In this group of patients other features commonly present are atrial fibrillation, advanced right heart failure, loud functional pulmonic murmurs, and other physical evidence of tricuspid incompetence.

SAGALL

Bucht, H., Ek, J., Eliasch, H., Thomasson, B., and Werko, L.: The Effect of a Single Intravenous Dose of Scillaren B on the Pulmonary Circulation and Renal Function in Patients with Rheumatic Heart Disease. Am. Heart J. **54**: 376 (Sept.), 1957.

The effect of a single intravenous dose of Scillaren B on the blood pressure in the lesser circulation and the clearance values of inulin and para-aminohippurate as well as sodium excretion were studied in 6 patients with rheumatic heart disease. The heart rate was found to decrease rapidly, in some cases during the first minute

after administration. The pulmonary blood pressure fell rapidly, while cardiac output remained unchanged. The stroke index rose considerably. No effect was noted on clearance values or sodium excretion. Compared with lanatoside C, Scillaren B acted with shorter latency on pulmonary pressures in patients with mitral stenosis, but did not show any of the prompt, direct renal effects of the digitalis drug. Scillaren B was found to be a rapidly acting potent cardiac drug with its renal action being secondary to the effect on the heart.

SAGALL

Balchum, O. J., Gensini, G., and Blount, S. G., Jr.: The Effect of Hexamethonium upon the Pulmonary Vascular Resistance in Mitral Stenosis. J. Lab. & Clin. Med. **50**: 186 (Aug.), 1957.

The administration of hexamethonium chloride via cardiac catheter to 15 patients with pulmonary hypertension at rest and supine resulted in a lowering of the brachial artery, pulmonary artery, and left atrial pressures; the cardiac output remained constant. The pulmonary arteriolar resistance decreased to a greater extent than either the total pulmonary or total peripheral resistances, suggesting the inhibition of pulmonary arteriolar vasoconstriction by hexamethonium. A second factor that may have been effective in lowering the pulmonary arterial pressure was a shifting of blood from the pulmonary to the systemic circuit as a result of the decrease in the total peripheral resistance. The marked increase in pulmonary artery pressure during exercise after hexamethonium administration may be related to the decreased volume and relative inelasticity of the pulmonary vascular bed but also to a closure of vascular pathways in the lungs, resulting in a greater resistance. A decrease in cardiac output during exercise was noted after hexamethonium administration as compared to the level before the giving of this drug.

MAXWELL

Oustrieres, G. O., Vernant, P., and Mathey, J.: Hemodynamics during Mitral Commissurotomy. Arch. mal. coeur **50**: 311 (April), 1957.

In 27 patients with mitral stenosis the left atrial, left ventricular, and sometimes also aortic pressures were registered with the same sensitivity and base line, together with the electrocardiogram, during mitral commissurotomy. This registration permitted direct calculation of the diastolic pressure gradient across the mitral valve as well as the mean surface of this gradient. In 17 patients this surface reached the normal value of 10 mm.^{2} after commissurotomy, while in 8 patients it decreased but did not reach this value, and in 2 patients it increased as a result of mitral regurgitation; in these latter a tall V wave and a holosystolic murmur appeared in the left atrial curve. Decrease of the gradient was accomplished in some of the patients by decrease of atrial pressure, while in the remainder a rise of diastolic ventricular pressure was also observed. This rise was evidently caused by traumatic injury of the left ventricle or by failure of this ventricle to adapt to the increased flow, since in 1 patient it could be abolished by injection of ouabaine.

LEPESCHKIN

Ebnother, C. L., Selzer, A., Stone, A. O., and Feichtmeir, T. V.: The Ventilatory Response to Exercise in Patients with Mitral Stenosis and Its Relationship to Circulatory Dynamics. Am. J. Med. Sc. **233**: 46 (Jan.), 1957.

Cardiopulmonary studies, including cardiac catheterization, in a series of patients with mitral stenosis demonstrated that patients with milder degrees of mitral stenosis show a normal ventilatory response to exercise by increasing the oxygen removal ratio with exercise to a degree only slightly less than do normal individuals. Those with severe mitral stenosis respond abnormally in that the oxygen removal ratio remains unaltered or falls with exercise. This abnormal response in the ventilation-oxygen consumption relationship could be correlated with the degree of dynamic alterations due to mitral stenosis as expressed by elevated pulmonary arterial and "wedge" pressures. The abnormal ventilatory response could not be correlated with the changes in cardiac output induced by exercise. The suggestion that changes in the oxygen removal ratio reflect an adequate or an inadequate increase in cardiac output during exercise is thus not confirmed. The altered ventilatory pattern is not directly related to hemodynamics in cardiac patients but rather is the effect of an alteration of the breathing mechanism that also causes dyspnea and that is thought to be due to changes in pulmonary compliance. The authors conclude that the change in total pulmonary ventilation in relation to oxygen consumption induced by exercise does not provide a specific test for various types of cardiac disorders. An abnormality in this ratio merely reflects an altered pattern of breathing that occurs frequently in patients with exertional dyspnea.

HARRIS

Braverman, I. B., and Gibson, S.: The Outlook for Children with Congenital Aortic Stenosis. Am. Heart J. **53**: 487 (April), 1957.

A series of 85 patients with congenital aortic

stenosis who were under the age of 16 years when first seen were studied in regard to state of health and cardiac symptoms. Follow-up data were available in 73. Of these patients 41 were completely asymptomatic, 26 had 1 or more cardiac symptoms and 6 under the age of 16 had died (5 suddenly). The case histories of those who had died are presented in detail. The high mortality rate found in this series leads the authors to conclude that congenital aortic stenosis is not as benign a condition as previously believed and selected cases should be considered for aortic valvulotomy. Based upon this study the principal indications for surgery would be the occurrence of syncope and easy fatigability, cardiac enlargement, and marked left heart strain.

SAGALL

Donald, K. W., Bishop, J. M., Wade, O. L., and Wormald, P. N.: Cardio-Respiratory Function Two Years after Mitral Valvotomy. Clin. Sc. **16**: 325 (May), 1957.

Previously reported studies of alterations in hemodynamics following surgical relief of mitral stenosis have been relatively few, and have been made at relatively short intervals after the operation. The authors therefore report observations on 28 patients made 17 to 51 months postoperatively, the mean period being 25 months. Nine of these patients were also studied at intervals of 6 to 12 months. Twenty-four of the patients showed great clinical improvement, despite mitral valve calcification, atrial fibrillation, rapid sedimentation rate, or heart failure. Improvement in the radiologic appearance of the heart and lung fields was less than expected. Only 4 patients showed reduction in pulmonary vascular shadows or disappearance of interlobular lines. Electrocardiographic changes were also infrequent. The outstanding finding was marked reduction in ventilation both at rest and after exercise, often to normal values. Another striking finding was reduction of right ventricular work at rest and, to a lesser extent, after exercise. Pulmonary arterial pressures and wedge pressures at rest were reduced in all but 2 patients, though they remained abnormally high. Pulmonary arterial pressures fell more than the wedge pressures. The latter became extremely elevated on exercise. Despite the marked clinical improvement, resting cardiac output was generally lower than before operation.

ENSELBERG

Pantridge, J. F., and Marshall, R. J.: Tricuspid Stenosis. Lancet **1**: 1319 (June 29), 1957.

Three cases of tricuspid stenosis, 2 already subjected to mitral valvulotomy, are presented and the clinical hemodynamic and surgical aspects are discussed. The symptoms are those associated with impaired cardiac filling. When the tricuspid stenosis is severe, it may mask the associated mitral disease. When it is moderate, the mitral disease dominates the picture and the tricuspid lesion may be unsuspected. Venous pressure is elevated and giant a waves may be found. Presystolic hepatic pulsation and cardiac cirrhosis may be noted. A rumbling diastolic murmur is heard at the left border of the sternum and a tricuspid opening snap may be present. The most striking feature is the presence of gross physical signs suggesting right ventricular failure in patients who are practically free of symptoms. Confirmatory evidence may be obtained from fluoroscopy, electrocardiography, and cardiac catheterization. An atrioventricular pressure gradient can be demonstrated. At operation, mitral obstruction should be dealt with before tricuspid valvulotomy to protect against pulmonary congestion. In 1 patient, an unusual degree of hypotension followed combined mitral and tricuspid operation.

KURLAND

Schaub, F., and Buhlmann, A.: Isolated Rheumatic Pulmonary Valvular Insufficiency. Ztsch. Kreislaufforsch. **46**: 320 (April), 1957.

A 38-year-old woman, who at the age of 4 had rheumatic polyarthritis and endocarditis, showed roentgenologically dilatation and vigorous pulsation of the pulmonary artery. The phonocardiogram showed an intense, diamond-shaped protodiastolic murmur, beginning after the second component of the split second heart sound, and localized in the left third interspace, while right bundle-branch block without signs of right ventricular hypertrophy was present in the electrocardiogram. The pulmonary arterial pressure curve showed a diastolic drop to zero; other pressure and oxygen values were normal. No signs of cardiac failure were present. This is the first published case of pulmonary regurgitation with rheumatic etiology.

LEPESCHKIN

Rewick, J., and Stewart, I.: Acquired Diverticulum of the Mitral Valve. Brit. M. J. **1**: 212 (Feb. 2), 1957.

In the last year of life a 63-year-old patient developed blindness from acute iridocyclitis, a loud blowing mitral systolic murmur and congestive heart failure. At autopsy the anterior mitral cusp "was distorted by a pouch large enough to accommodate the tip of the little finger to a depth of over 1 cm. The pouch was directed

backwards so that during ventricular systole it would impinge on the posterior cusp as a round ball, leaving a triangular orifice on either side." The pathogenesis was obscure.

McKusick

Fejfar, Z.: Cardiac Output and Its Regulation. Acta Cardiol. **12**: 13 (Jan.), 1957.

In 53 patients with mitral stenosis of various degrees the cardiac output was determined by the Fick method before and after inhalation of pure oxygen. In cases with a cardiac index higher than 2.61, no change occurred. However, a statistically significant rise of cardiac output was observed in patients with cardiac indices below 2.61, and this was independent of the pulmonary arterial pressure and the level of the original arterial oxygen saturation. The result suggests that oxygen inhalation may improve cardiac efficiency in patients with reduced cardiac output, which is in keeping with Harrison's hypothesis concerning the role of myocardial oxygen tension in the regulation of cardiac output.

Pick

Heeger, H., and Polzer, K.: Study of Liver Pulsations in Tricuspid Insufficiency. Cardiologia **30**: 245 (April), 1957.

The authors present pulse curves recorded by their method (rheography) from the hepatic region in normal individuals and in patients with tricuspid regurgitation. In the latter, the hepatorheogram revealed pronounced diastolic variations ascribed to congestion associated with pulsation. An alternative interpretation, viz., direct regurgitation waves was rejected on the basis of comparison of synchronous pulse curves obtained from the right and left side of the liver that gave mirror-image patterns. This divergence of the pulsations can be explained by the well-known see-saw movement of the thorax and hence is attributable to mechanical impulses originating in the heart itself. In support of their views, the authors consider the regression of diastolic pulse phenomena subsequent to ligation of the inferior vena cava in some patients.

Pick

Black, H., and Harken, D. E.: Current Indications for the Surgical Correction of Mitral Stenosis. Am. Heart J. **53**: 439 (March), 1957.

Advances in diagnosis, in preoperative and postoperative care and in technic have reduced the operative mortality of mitral valvuloplasty for mitral stenosis to less than 1 per cent in patients who have not progressed to irreversible congestive heart failure. Accordingly, operation can be advised routinely for patients with symptomatic mitral stenosis, for in these patients the risk of operation is far less than the danger of the disease. Because of the marked increase in operative mortality when refractory congestive failure has developed, patients should not be allowed to reach such a phase of their disease when relief by surgery is available earlier at such a low risk. An age over 50, atrial fibrillation, moderate mitral insufficiency, associated valvular disease and suspected rheumatic activity are no longer considered as absolute deterrants to operation.

Sagall

Schirosa, G.: Angina in Mitral Disease. Clinical and Electrocardiographic Study with Intraventricular Pressure. Cardiologia **30**: 18 (Nov. 1), 1957.

Clinical, hemodynamic, and electrocardiographic observations are reported in 2 female patients (21 and 26 years old) with rheumatic mitral disease suffering from precordial pain on effort or emotion. Electrocardiograms after exercise showed changes characteristic of acute coronary insufficiency while simultaneous pressure recordings revealed an increase in right ventricular hypertension. The pathogenesis of angina in mitral valvular disease can be explained on the basis of a sudden disproportion between coronary blood flow and work of the left ventricle resulting in relative myocardial ischemia. The attacks are precipitated by a sudden aggravation of pressure elevation in the lesser circulation leading to an increase in the work of the heart, which in turn demands increase of coronary flow. If this adaptation fails, an attack of angina results.

Pick

Daugavietis, H. E., and Mautner, L. S.: Disseminated Nodular Pulmonary Ossification with Mitral Stenosis. Arch. Path. **63**: 7 (Jan.), 1957.

A case of disseminated nodular pulmonary ossification in association with mitral stenosis is described. The patient was a 30-year-old man who presented typical findings of rheumatic heart disease with mitral stenosis and insufficiency and who pursued a downhill course to death in 3 years. On x-ray, his lungs showed multiple, small, dense opacities, measuring up to 8 mm. in diameter, throughout both lung fields. At autopsy these were proved to be bony nodules occupying the air spaces of the lungs without associated degenerative, inflammatory or proliferative vascular changes. Pulmonary ossifications are rare, and occur in association with rheumatic heart disease and mitral stenosis. They occur mostly in young adults, with a predominance of males. The pathogenesis is unclear.

Maxwell

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AHA SCIENTIFIC SESSIONS: DEADLINE FOR ABSTRACTS IS JUNE 13, 1958

The Heart Association urges submission of abstracts of scientific papers to be selected for the 31st Annual Scientific Sessions of the Association in San Francisco, October 24-26.

Deadline is June 13, 1958.

Papers intended for presentation should be based on original investigations in or related to the cardiovascular field. Abstracts should be limited to 250 words. They must be submitted on forms available from F. J. Lewy, M.D., Assistant Medical Director, American Heart Association, 44 East 23rd Street, New York 10, N.Y.

The Scientific Sessions will present a section for scientific and industrial exhibits. Requests for space for scientific exhibits must be made on application forms obtainable from Dr. Lewy. Applications must be submitted not later than June 13, 1958. Applications for industrial exhibits may be requested through Steven K. Herlitz, Inc., 280 Madison Avenue, New York 16, N. Y.

AHA SCIENTIFIC SESSIONS SCHEDULE IS OUTLINED

The following tentative schedule has been decided on by the Program Committee for the 31st Annual Scientific Sessions of the American Heart Association, to be held at the Civic Center, San Francisco, from Friday, October 24 through Sunday, October 26:

Friday, October 24

The opening session on Friday morning will be on the subject of genetics, keyed to the general interest of physicians. It will be presented jointly by the Heart Association and the American Society for the Study of Arteriosclerosis. This year for the first time the Society is holding its Annual Meeting to coincide with the AHA Scientific Sessions. Additional sessions on Friday morning will be sponsored by the Heart Association's Councils on Circulation and on Cardiovascular Surgery.

Friday afternoon will be devoted to a session sponsored by the Council on Rheumatic Fever and Congenital Heart Disease and to a Symposium conducted jointly by the Heart Association's Council on Circulation and the Microcirculatory Conference. On Friday evening a session will be conducted on "Instrumental Study of the Heart and Circulation," to be chaired jointly by Charles E. Kossmann, M.D., Associate Professor of Medicine, New York University College of Medicine, and Victor McKusick, M.D., Assistant Professor of Medicine, Johns Hopkins University School of Medicine.

Practicing Physicians' Sessions

Concurrently, on Friday, an all-day session for practicing physicians will be held under sponsorship of the Council on Clinical Cardiology. Presented last year for the first time, this is essentially a presentation of clinical problems in cardiovascular disease and has again been classified by the American Academy of General Practice as acceptable for Category II credit for Academy members.

Saturday, October 25

Scheduled for Saturday morning are: A session on Applied Cardiovascular Research; the George E. Brown Memorial Lecture by Lewis Thomas, M.D., Professor and Chairman, Department of Pathology, New York University College of Medicine; the Lewis

A. Conner Memorial Lecture; and the presentation of the Albert Lasker Award of the American Heart Association for cardiovascular research.

On Saturday afternoon, joint Panels on "Emotional and Endocrine Aspects of Cardiovascular Disease" and "Effects of Hemodynamics and Vascular Injury" will be presented in conjunction with the American Society for the Study of Arteriosclerosis.

Sunday, October 26

Sunday morning's schedule includes sessions to be conducted simultaneously by the Councils on Clinical Cardiology, High Blood Pressure Research, and Basic Science. Featured on Sunday afternoon will be a special program on "Rewards of Research," designed to interest laymen as well as physicians. This program, sponsored by the Council on Community Service and Education, will consist of a panel discussion between research scientists and science writers. In addition, a program on "Prevention of Rheumatic Fever" is scheduled for Sunday afternoon.

The Association's Annual Dinner, at which a number of awards will be presented, will be held on Sunday evening.

Annual Meeting of Assembly

The Annual Meeting of the Assembly will begin Monday morning, October 27. Six Assembly Panels will be in session throughout the day. The panels and their chairmen will be: Research, Howard B. Buchell, M.D., Mayo Clinic, Rochester, Minn.; Fund Raising and Public Relations, John D. Brundage, Montclair, N. J., Acting Chairman of the AHA Board; Relationships and Responsibilities Between National, State and Local Heart Associations, Merritt H. Stiles, M.D., Spokane, Wash., member of the AHA Board; Community Service—Screening and Case Finding Programs, Edward M. Cohart, M.D., Department of Public Health, New Haven, Conn., and a member of the AHA Board; The Physician's Continuous Self-Education, Stewart G. Wolf, M.D., University of Oklahoma School of Medicine, Oklahoma City; and Membership, Jerome G. Kaufman, M.D., Newark, N. J., member of the AHA Board.

The meeting of the General Assembly on Tuesday morning, October 28, will open with a keynote address by William P. Shepard, M.D., 2nd Vice President, Health and Welfare Division, Metropolitan Life Insurance Company.

The Annual Scientific Sessions and Annual Meeting coincide with the 10th Anniversary of the Association as a national voluntary health agency.

HAWAII SCIENTIFIC SESSIONS

Physicians and scientists attending the Association's Scientific Sessions in San Francisco have been invited by the Hawaii Heart Association to participate in a post-meeting tour which includes two days of scientific sessions. Arrangements for attending should be made through H. Douglas Chisholm, Associate Director, American Heart Association, 44 East 23rd Street, New York, N. Y., or directly through the American Express Company, 65 Broadway, New York, N. Y.

ASSA ABSTRACTS DUE MAY 31

May 31, 1958 is the deadline for submitting abstracts of papers to be presented at the Annual Meeting of the American Society for the Study of Arteriosclerosis in San Francisco, October 24-26. Abstracts should be sent in quadruplicate to Forrest Kendall, Ph.D., Goldwater Memorial Hospital, Welfare Island 17, N. Y. The Society is holding its meeting simultaneously with the Scientific Sessions of the American Heart Association. Several joint programs have been planned.

NEW CV RESEARCH INSTITUTE

Opening day ceremonies for the new Cardiovascular Research Institute of the University of California Medical Center will be held on Thursday, October 23, preceding the AHA Scientific Sessions in San Francisco, October 24-26. Physicians and scientists have been invited to attend the ceremonies to see the Institute's modern facilities for research and to review its program.

WORLD CARDIOLOGY CONGRESS SYMPOSIA SUBJECTS LISTED

In addition to presenting a great many papers at the Third World Congress of Cardiology in Brussels, Belgium, September 14-21, physicians and scientists from all over the world will participate in a variety of symposia and round-table discussions.

Subjects for Symposia include: Physiology; Cardiac Failure, Local Circulation; Peripheral Circulation; Coronary Circulation; Pulmonary Circulation; Arteriosclerosis; Hypertension; Collagen Diseases; Correlation of Electrocardiographic and Pathologic Observations; Diagnosis of Coronary Diseases; Normal Limits and Functional Modifications of the ECG; Vectorial Electrocardiography; Radiological Methods; Congenital Heart Diseases; Acquired Valvular Diseases; Geographic Epidemiology; and Social Cardiology.

Subjects for the Round-Table discussions will be listed in forthcoming issues of *Circulation* and *Circulation Research*.

LOCAL STATIONS TO SHOW NBC-TV RESEARCH SERIES

Several affiliated stations of the NBC-TV network have scheduled the showing of kinescopes during May and June of the series "Decision for Research," designed to interest young people in careers as research investigators in the medical and biological sciences. The series is being presented by NBC-TV and the American Heart Association in cooperation with the Educational Television and Radio Center. The half-hour programs in the 13-week series are now being telecast "live" over Educational Television stations. They were assisted by a grant from E. R. Squibb and Sons, a division of Olin Mathieson Chemical Corporation.

NEVADA HEART ASSOCIATION

With formation recently of the Nevada Heart Association as an affiliate of the American Heart Association, every state in the union is now represented among the Association's 57 direct affiliates which also include the District of Columbia, Puerto Rico, Alaska and Hawaii. Peter Rowe, M.D., of Reno, has been chosen as President of the Nevada Heart Association.

NEW DIET LEAFLET

A new leaflet available for distribution by physicians to their patients, "What We Know About Diet and Heart Disease," has been published by the Heart Association. Consisting of answers to questions most frequently asked on this subject, the leaflet is available from the American Heart Association, 44 East 23rd Street, New York 10, N. Y. or from local Heart Associations.

HYPERTENSION PROCEEDINGS ON MINERAL METABOLISM NOW AVAILABLE

The Proceedings of the Annual Meeting of the Council on High Blood Pressure Research, which contained an up-to-date symposium on mineral metabolism as related to arterial hypertension, have been published. The Council met in November, 1957.

The 109-page, illustrated volume also contains discussions by leading authorities in their fields on such subjects as *"The Relationship of Sodium, Potassium and Water Ratios to Hypertension," "The Exploration of the Renal Excretory Mechanism with Radioactive Sodium and Potassium,"* and an important clinical syndrome, *"Chronic Sodium Chloride Toxity and the Protective Effect of Potassium Chloride."*

Also included in the volume are committee reports on the current status of surgical treatment, chemotherapy, epidemiology of hypertension and instrumental techniques.

The volume, sixth in a series on Hypertension based on the Council's annual meetings, is obtainable through the American Heart Association, 44 East 23rd Street, New York 10, N. Y. or through local Heart Associations at $2.50 a copy. A special pre-publication rate of $2.00 a copy will be given for orders received before June 1, 1958.

CALCULUS COURSE IN MAINE

A two-week postgraduate course in "Calculus for Research Workers" will be sponsored by the Maine Heart Association at Bowdoin College, Brunswick, Me., July 14-25. An introductory course for research investigators in the medical and biological sciences, it will be conducted by Richard Chittim, Professor of Mathematics at Bowdoin College. Fee for the course is $75, plus moderate living costs. Further information may be obtained from Dr. Clifford V. Nelson, Maine Medical Center, Portland, Me.

MEETINGS CALENDAR

May 28-June 14: 11th World Health Assembly, World Health Organization, Minneapolis. WHO, Palais des Nations, Geneva, Switzerland.

June 21: International Cardiovascular Society, North American Chapter, San Francisco. Henry Haimovici, M.D., 105 East 90th Street, New York 28, N. Y.

June 23-27: American Medical Association, San Francisco. George F. Lull, 535 N. Dearborn, Chicago 10, Ill.

August 11-14: National Medical Association, Milwaukee. John T. Givens, 1108 Church Street, Norfolk 10, Va.

August 24-29: Congress of Physical Medicine and Rehabilitation, Philadelphia. Frances Baker, 1 Tilton Street, San Mateo, Calif.

October 6-10: American College of Surgeons, Chicago. Michael L. Mason, 40 E. Erie Street, Chicago 11, Ill.

October 24-28: American Heart Association 31st Annual Scientific Sessions, San Francisco. American Heart Association, 44 East 23rd Street, New York 10, N. Y.

October 27-31: American Public Health Association, St. Louis. Berwyn F. Mattison, 1790 Broadway, New York 19, N. Y.

ABROAD

June 15-19: Canadian Medical Association, 91st Annual Meeting, Halifax, Nova Scotia. Canadian Medical Association, 244 George Street, Toronto 5, Canada.

September 14-21: Third World Congress of Cardiology, Brussels. Dr. F. Van Dooren, 80 Rue Mercelis, Brussels, Belgium.

September 22-28: 16th International Congress of History of Medicine, Montpellier, France. Louis Dulieu, M.D., Montpellier, (Herault) France.

September 25-28: Third International Congress of Angiology, Venice, Italy. M. Comel, M.D., Dermatological Clinic, University of Pisa, Pisa, Italy.

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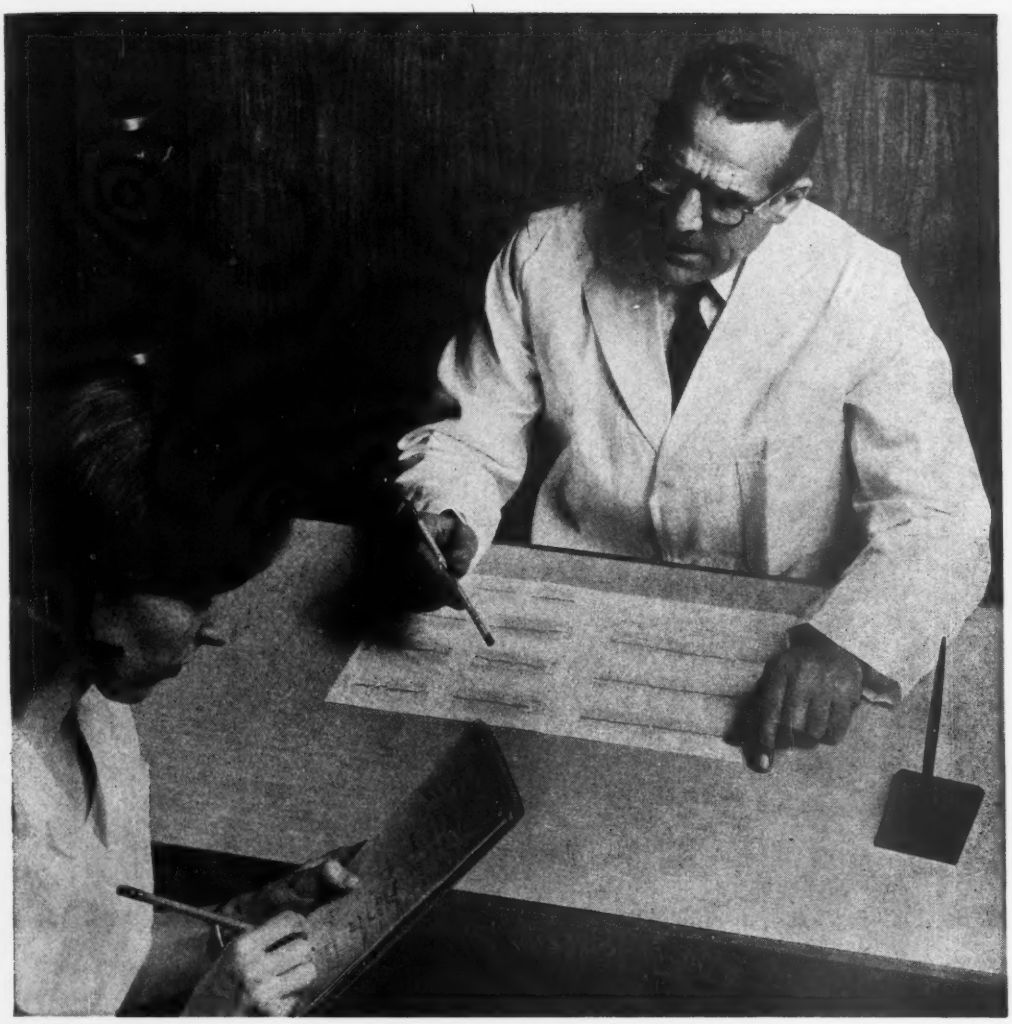

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